

LIPOBAY 400 microgram tablets

Summary of Product Characteristics (describing) **Composition and Form:** Red tablets: Lipobay® 400 Microgram contain 381.7mcg cerivastatin in the form of 400mcg cerivastatin sodium.

Therapeutic indications: Primary hypercholesterolaemia (Types IIA + IIB): The treatment of hypercholesterolaemia in who have not responded adequately to an appropriate diet. **Posology and administration:** Exclude secondary causes of hypercholesterolaemia prior to therapy. A standard cholesterol-lowering diet may be enhanced in combination

with a bile-acid sequestrant (e.g. colestyramine). **Adults:** Take once a day in the evening, with or without food. Start at 100mcg and titrate by 100mcg depending on response at four week intervals. Maximum dose of 400mcg. **Elderly:** Treatment should be initiated at the lower end of the dose range. **Moderate to severe renal impairment:** Start at 100mcg and titrate with caution. Maximum dose of 200mcg once daily. **Children:** Not recommended. **Contraindications:** Hypersensitivity; myopathy, impairment or unexplained, persistent elevations in serum transaminases; pregnancy or lactation. Women of childbearing potential should use non-oral contraceptive methods. **Warnings and precautions:** **Liver function:** Increases serum enzymes and, very rarely, cases of liver disease (mostly minor and asymptomatic) have occurred. Liver function tests are recommended. Discontinue therapy if ALT and AST >3xULN. Caution in patients with a history of heavy alcohol consumption or liver disease. **Muscle:** Sporadic CPK elevations, not usually clinically significant, have been observed. Rarely, myopathy, associated with marked elevations of CPK (>10xULN) and/or with diffuse muscle tenderness or weakness, has been reported. Patients should report symptoms, especially if accompanied by fever. Discontinue if markedly elevated CPK levels occur, or if myopathy is suspected. Risk of myopathy is increased on concomitant administration with cyclosporin, fibric acid derivatives, nifedipine, itraconazole and nicotinic acid.

Interactions: Risk of rhabdomyolysis (some with acute renal failure secondary to myoglobinuria) in combination with gemfibrozil and, very rarely, with cerivastatin monotherapy. Withhold Lipobay® temporarily from patients experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis.

Pharmacological: New subcapsular and nuclear opacities have been reported, but a causal relationship with Lipobay® has not been established. **Interactions:** **Drugs known not to interact with cerivastatin:** Warfarin, digoxin, nifedipine, ibuprofen, omeprazole, cimetidine and antacids. **Drugs that interact with cerivastatin:** Erythromycin, itraconazole, cyclosporin, gemfibrozil and bile acid sequestrants. Rifampicin or phenytoin effects are unknown. **Undesirable effects:** Abdominal pain, allergic reaction, angioedema, arthralgia, asthenia, constipation, diarrhoea, dyspepsia, eye disorders, flatulence, headache, hepatitis, increased CPK, insomnia, leg and arm pain, myalgia, myasthenia, myositis, nausea, paresthesia, rash, rhabdomyolysis and Mostly mild transaminase (ALT/AST) increases. **Legal category:** POM. **Package sizes and basic NHS costs:** Calendar pack containing 28 tablets; Lipobay® 400 microgram Tablets £17.35. **Marketing authorisation number:** PL 00010/0249. **Date of Preparation:** November 1999. For further information refer to Summary of Product Characteristics or contact: Bayer plc, Pharmaceutical Division, Newbury, Berkshire, RG14 1JA (01353) 563000. © Bayer plc June 2000

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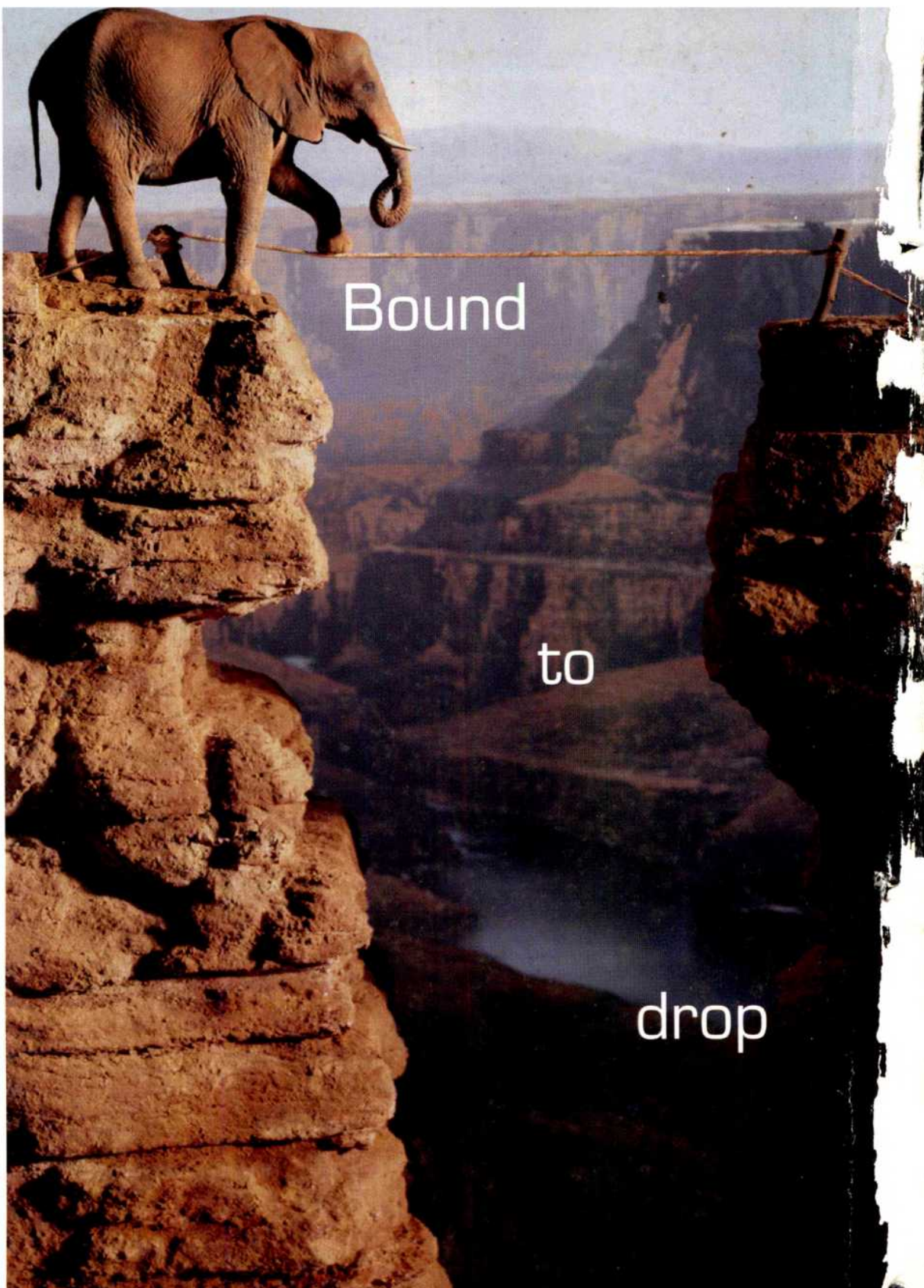
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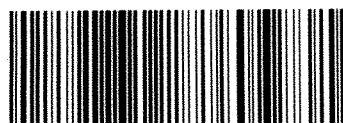
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Martin S. Karpeh, MD Congress Secretariat	

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British Journal of Surgery

Volume 87, Issue 10, October 2000

Leading article

- 1281 **Medical management of bowel obstruction**

J. R. Hardy

If death is inevitable

Surgical publishing

- 1284 **Politics in surgical publishing**

C. J. Laitman and L. F. Rikkers

- 1287 **COPE — Guidelines on good publication practice**

Reviews

- 1288 **Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon**

I. Lindsey, R. J. Guy, B. F. Warren and N. J. McC. Mortensen

A classification of dissection planes is proposed

- 1300 **Vascular access for haemodialysis**

G. J. Murphy, S. A. White and M. L. Nicholson

Fewer new fistulas and more revisional procedures

- 1316 **Factors predictive of outcome after surgery for faecal incontinence**

M. K. Baig and S. D. Wexner

The many options are examined and an algorithm for treatment is presented

Digest

- 1331 **Surgery Today**

S. Matsuno

Association of Surgeons

- 1336 **Hypertonic saline attenuates end-organ damage in an experimental model of acute pancreatitis**

C. J. Shields, D. C. Winter, S. Sookkai, L. Ryan, W. O. Kirwan and H. P. Redmond

A clinical trial may now be justified

- 1341 **Chronic dysphagia following laparoscopic fundoplication**

J. R. Bessell, R. Finch, D. C. Gotley, B. M. Smathers, L. Nathanson and B. Menzies

No evidence that a tailored approach offers any advantage

- 1346 **Interleukin 10-deficient colitis: new similarities to human inflammatory bowel disease**

R. J. Kennedy, M. Hoper, K. Deodhar, P. J. Erwin, S. J. Kirk and K. R. Gardiner

Another useful model for colitis

- 1352 **Randomized clinical trial of sutured *versus* stapled closed haemorrhoidectomy**

K. H. Khalil, A. O'Bichere and D. Selhu

Better short-term results from stapled haemorrhoidectomy

- 1356 **Causes of re-recurrence after polytetrafluoroethylene patch saphenoplasty for recurrent varicose veins**

T. S. Bhatti, B. Whitman, K. Harradine, S. G. Cooke, B. P. Heather and J. J. Earnshaw

Where do the recurrent veins come from?

- 1361 **Short-term results of femoropopliteal subintimal angioplasty**

R. J. McCarthy, W. Neary, C. Roobottom, A. Tottle and S. Ashley

Not encouraging

Randomized clinical trials

- 1366 **Multicentre, randomized clinical trial of primary *versus* secondary sigmoid resection in generalized peritonitis complicating sigmoid diverticulitis**

G. Zeitoun, A. Laurent, F. Rouffet, J.-M. Hay, A. Fingerhut, J.-C. Paquet, C. Peillon and the French Associations for Surgical Research

Primary resection is superior to secondary resection

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J.A. Norton,
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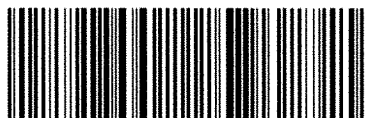
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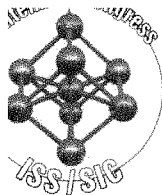
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Original articles

- 1375 **Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis**
J. J. Powell, J. T. Murchison, K. C. H. Fearon, J. A. Ross and A. K. Siriwardena
 Enteral nutrition does not ameliorate the acute inflammatory response
- 1382 **Preventive effect of preoperative portal vein ligation on endotoxin-induced hepatic failure in hepatectomized rats is associated with reduced tumour necrosis factor α production**
S. Yachida, K. Ikeda, K. Kaneda, F. Goda, T. Maeba and H. Maeta
 Portal vein ligation is associated with diminished TNF- α production during liver regeneration
- 1391 **Localization of matrix metalloproteinase 2 within the aneurysmal and normal aortic wall**
M. Crowther, S. Goodall, J. L. Jones, P. R. F. Bell and M. M. Thompson
 Further characterization of the causes of aneurysm formation
- 1401 **Factors influencing the functional outcome of restorative proctocolectomy in ulcerative colitis**
U. Karlbom, Y. Raab, S. Ejerblad, W. Graf, M. Thörn and L. Pålman
 Prevention of late complication most important
- 1409 **Raised levels of plasma Big Endothelin 1 in patients with colorectal cancer**
R. A. Simpson, T. Dickinson, K. E. Porter, N. J. M. London and D. M. Hemingway
 Patients with metastases have elevated levels
- 1414 **Clinical presentation of the pseudomyxoma peritonei syndrome**
J. Esquivel and P. H. Sugarbaker
 Early recognition would facilitate potential curative treatment
- 1419 **Recurrent sigmoid volvulus treated by percutaneous endoscopic colostomy (short note)**
I. R. Daniels, M. J. Lamparelli, H. Chave and J. N. L. Simson
 A minimally invasive technique for sigmoid volvulus
- 1420 **Effect of surgical subspecialization on breast cancer outcome**
J. Golledge, J. E. Wiggins and M. J. Callam
 Significantly improved outcome in this retrospective review
- 1426 **Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy**
S. M. Dresner and S. M. Griffin
 Better staging procedures still required
- 1434 **Major intra-abdominal pathology missed at laparoscopic cholecystectomy (short note)**
A. J. Malouf, A. W. Murray and A. B. MacGregor
 A diagnostic laparoscopy procedure may reduce the 0.6% of patients who have 'missed' serious intra-abdominal pathology during laparoscopic cholecystectomy
- 1436 **Correspondence**
- 1437 **Book reviews**
- 1438 **Scientific surgery**
- 1439 **Instructions to authors**



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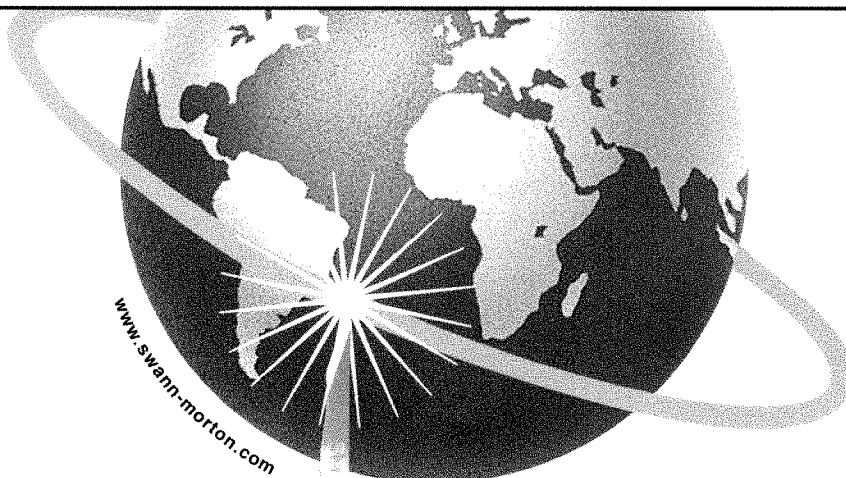
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British Journal of Surgery

Volume 87, Issue 11, November 2000

Leading article

- 1441 **Living donor liver transplantation: present and future**

J. Belghiti and F. Durand

A consensus view on the ethics involved is needed

Surgical publishing

- 1444 **On the editor's desk**

J. R. Farrdon and J. A. Murie

- 1448 **Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement**

D. Mober, D. J. Cook, S. Eastwood, I. Olkin, D. Rennie and D. F. Stroup, for the QUOROM group

Reviews

- 1455 **Immediate breast reconstruction after mastectomy for cancer**

C. M. Malata, S. A. McIntosh and A. D. Purushotham

A safe and acceptable procedure

- 1473 **Duodenal injuries**

E. Degiannis and K. Boffard

The incidence is increasing

- 1480 **Postoperative ileus: a preventable event**

K. Holte and H. Keblet

A multimodal approach is advocated

Original articles

- 1494 **Operative treatment of pseudocysts in patients with chronic pancreatitis**

V. Usatoff, R. Brancatisano and R. C. N. Williamson

A personal surgical series including 112 consecutive patients

- 1500 **Surgical treatment of adult primary hepatic sarcoma**

J. L. Poggio, D. M. Nagorney, A. G. Nascimento, C. Rowland, P. Kay, R. M. Young and J. H. Donohue

Surgical resection is the only effective therapy

- 1506 **Endoscopic stent placement for pancreaticocutaneous fistula after surgical drainage of the pancreas**

D. Boerma, E. A. J. Rauws, T. M. van Gulik, K. Huibregste, H. Obertop and D. J. Gouma

Early ERP and stent insertion facilitates closure of pancreaticocutaneous fistulas

- 1510 **Effects of hepatic blood inflow occlusion on liver regeneration following partial hepatectomy in an experimental model of cirrhosis**

X.-Y. Yin, P. B. S. Lai, J. F. Y. Lee and J. W. Y. Lau

Hepatic inflow occlusion does not affect liver regeneration or survival following partial hepatectomy

- 1516 **Compliance properties of conduits used in vascular reconstruction**

N. R. Tai, H. J. Salacinski, A. Edwards, G. Hamilton and A. M. Seifalian

The search for a small calibre prosthesis for vascular reconstruction goes on

- 1525 **Safety of a single duplex scan to exclude deep venous thrombosis**

B. Wolf, D. M. Nichols and J. L. Duncan

A study including 537 patients with suspected DVT

- 1529 **Vasoactive and proliferative effects of parathyroid hormone and parathyroid hormone-related peptide on human vascular smooth muscle**

D. R. Chadwick, B. J. Harrison, P. Chan, L. Chong and P. Peachell

Desensitization to PTHrP not a cause of cardiovascular disease in hyperparathyroidism

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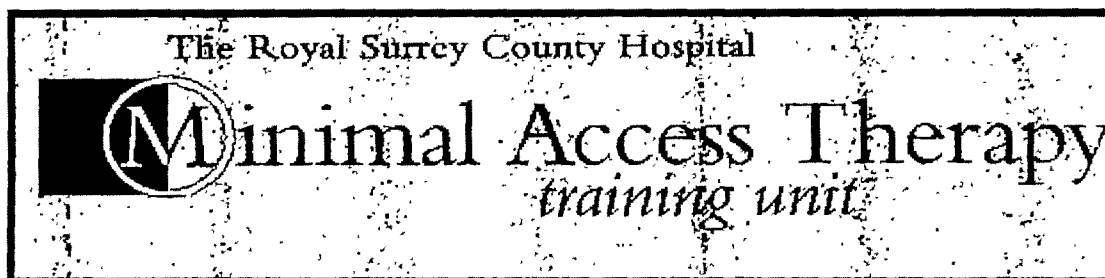
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- 1534 **Experimental model of anorectal transplantation**
A. O'Bichere, S. Sburey, P. Sibbons, C. Green and R. K. S. Phillips
 Proof in principle that this model works
- 1540 **Rapid rehabilitation in elderly patients after laparoscopic colonic resection**
L. Bardram, P. Funch-Jensen and H. Kehlet
 Multimodal rehabilitation leads to early discharge
- 1546 **Results of surgical treatment for faecal incontinence**
A. Osterberg, K. Edebol Eeg-Olofsson and W. Graf
 Anterior levatorplasty and sphincteroplasty yield similar results in selected patients
- 1553 **Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer**
T. Mynster, I. J. Christensen, F. Moesgaard and H. J. Nielsen for the Danish RANX05 Colorectal Cancer Study Group
 The combination rather than individual factors seem to be important
- 1563 **Tacrolimus has less fibrogenic potential than cyclosporin A in a model of renal ischaemia-reperfusion injury**
S. Jam, G. R. Bicknell and M. L. Nicholson
 May be a better immunosuppressant in the long term
- 1569 **Differential effects of cyclosporin and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants**
G. R. Bicknell, S. T. Williams, J. A. Shaw, J. H. Pringle, P. N. Furness and M. L. Nicholson
 Tacrolimus less fibrogenic than cyclosporin
- 1576 **Jejunal interposition to prevent postgastrectomy syndromes**
Y. Morii, T. Arita, K. Shimoda, K. Yasuda, Y. Matsui, M. Inomata and S. Kitano
 Jejunal interposition reduced the rate of dumping in this review including 42 patients
- 1580 **Role of resection and primary anastomosis of the left colon in the presence of peritonitis**
S. Biondo, E. Jaurrieta, J. Martí Ragué, E. Ramos, M. Deiros, P. Moreno and L. Farran
 Resection and primary anastomosis is safe in selected patients
- 1585 **Ten-year audit of randomized trials in digestive surgery from Europe (short note)**
K. Skm, M. Haugb, P.-L. Fagniez, D. Pezet and J. Chipponi
 Evidence for increasing enthusiasm among gastrointestinal surgeons
- 1587 **Results of treatment of 33 patients with peritoneal mesothelioma**
G. Sebbag, H. Yan, B. M. Shmookler, D. Chang and P. H. Sugarbaker
 Radical cytoreductive surgery plus intraperitoneal chemotherapy may extend survival but with significant morbidity
- 1594 **Correspondence**
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British Journal of Surgery

Volume 87, Issue 12, December 2000

Leading article

- 1601 **Non-intervention and palliative care in vascular patients**

W. B. Campbell

Technical ability must be tempered with common sense

Surgical publishing

- 1603 **Dealing with the rejected article**

P. J. Guillou and J. J. Earnshaw

- 1605 **Research misconduct: diagnosis, treatment and prevention**

M. J. G. Farthing

- 1610 **Epilogue: key considerations in surgical publishing**

M. Schein, J. R. Farndon and A. Fingerhut

Clinical dilemma

- 1615 **Liver fracture and bleeding**

J. E. J. Krige

Initial management is critical

Reviews

- 1617 **Neosphincters in the management of faecal incontinence**

D. A. Niriella and K. I. Deen

Recent technical advances are discussed

- 1629 **Biological behaviour and clinical implications of micrometastases**

M. R. Kell, D. C. Winter, G. C. O'Sullivan, F. Shanahan and H. P. Redmond

The concept of micrometastases has resulted in a paradigm shift in the staging of epithelial tumours

- 1640 **Role of surgery in mild primary hyperparathyroidism in the elderly**

N. A. Roche and A. E. Young

Surgery is beneficial for those who have symptoms

Original articles

- 1650 **Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis**

S. A. Norton and D. Alderson

Essential in the diagnosis of 'idiopathic' pancreatitis

- 1656 **Biliary fistula associated with gallbladder carcinoma (short note)**

H. Nishio, J. Kamiya, M. Nagino, K. Uesaka, T. Sano and Y. Nimura

Preoperative diagnosis important

- 1658 **Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population**

T. M. Kennedy and R. H. Jones

IBS may cause diagnostic confusion

- 1664 **Appendicectomy and perioperative mortality in patients with liver cirrhosis (short note)**

The late L. O. Poulsen, A. M. Thulstrup, H. T. Sørensen and H. Vilstrup

Perioperative mortality is increased

- 1666 **Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR)**

R. J. F. Laeij, J. Buth, P. L. Harris, F. L. Moll, W. J. Stelter, E. L. G. Verboeven on behalf of the EUROSTAR collaborators

Reinterventions needed at a rate of 10 per cent per year



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- 1674 **Gender differences in the longitudinal pressure profile of the anal canal related to anatomical structure as demonstrated on three-dimensional anal endosonography**
A. B. Williams, M. J. Cheetam, C. I. Bartram, S. Halligan, M. A. Kamm, R. J. Nicholls and W. A. Kmiot
 New technique gives insight into complex anatomy
- 1680 **Endorectal flap advancement repair and fistulectomy for high trans-sphincteric and suprasphincteric fistulas**
H. Ortiz and J. Marzo
 An effective technique for difficult anal fistula
- 1684 **Mitogenic effects of oestrogen mediated by a non-genomic receptor in human colon**
D. C. Winter, C. Taylor, G. C. O'Sullivan and B. J. Harvey
 Oestrogen is mitogenic via a PKC-mediated mechanism
- 1690 **Hyaluronic acid as prognostic marker in resectable colorectal cancer**
A. LLaneza, F. Vizoso, J. C. Rodríguez, P. Raigoso, J. L. García-Muñiz, M. T. Allende and M. García-Morán
 High cytosolic levels associated with a poor prognosis
- 1697 **Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease**
O. Bernell, A. Lapidus and G. Hellers
 Large study of risk factors for surgery and recurrence
- 1702 **Risk factors related to operative mortality and morbidity in patients undergoing emergency gastrectomy**
J. B. Y. So, A. Yam, W. K. Cheab, C. K. Kum and P. M. Y. Gob
 Confirms the accepted criteria of age, anaesthesia and hypotension
- 1708 **Day-case laparoscopic fundoplication for gastro-oesophageal reflux disease**
E. Trondsen, O. Mjåland, J. Raeder and T. Buanes
 Safe and acceptable to most patients
- 1712 **Clinicopathological study of multiple superficial oesophageal carcinoma**
A. Kanamoto, H. Yamaguchi, Y. Nakanishi, Y. Tachimori, H. Kato and H. Watanabe
 High-risk factors are identified
- 1716 **Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma**
A. G. E. M. de Boer, P. I. Onorbe Genovesi, M. A. G. Sprangers, J. W. van Sandick, H. Obertop and J. J. B. van Lanschot
 Survivors have a good quality of life
- 1722 **Groin hernia repair in Scotland**
A. Hair, K. Duffy, J. McLean, S. Taylor, H. Smith, A. Walker, I. M. C. Macintyre and P. J. O'Dwyer
 Open mesh is the repair of choice in Scotland
- 1727 **Future of laparoscopic inguinal hernia surgery (short note)**
D. K. Beattie, R. J. E. Foley and M. J. Callam
 The future looks rather gloomy
- 1729 **The Seldinger technique for difficult transurethral catheterization: a gentle alternative to suprapubic puncture (short note)**
M. L. Lachat, U. Moebrlen, H. P. Bruetsch and P. R. Vogt
 Useful technique for difficult catheterization

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Enteral *versus* parenteral nutrition

J. MacFie

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Artificial feeding is indicated for patients with pre-existing malnutrition or for those whose oral intake is anticipated to be inadequate for 7 days or more¹. Not surprisingly, most authorities recommend the enteral as opposed to the parenteral route. Enteral is considered cheaper and safer, and more physiological in that it preserves gut barrier function. Parenteral, in contrast, may result in mucosal atrophy, bacterial translocation and increased rates of septic morbidity. There is experimental evidence to support these views but what of clinical research?

Enteral nutrition is certainly cheaper than parenteral. The average daily cost of a standardized parenteral feed is approximately eight times more than that of an equivalent enteral feed, assuming similar protein and energy intakes. This cost, however, does not take into account delivery systems or associated complications. The increasing propensity of clinicians to employ invasive methods of delivery for enteral nutrition may well offset perceived cost benefits. Few studies have specifically addressed the additional costs related to nutrition-related morbidity.

There is no doubt that enteral nutrition can be provided safely and effectively for prolonged periods. However, it is increasingly recognized that it often fails to achieve targeted calorie requirements, particularly in critically ill patients². This is often a consequence of poor tolerance, manifested by bloating, diarrhoea or continued high-volume nasogastric aspirates. None the less, there may be benefits attributable to enteral nutrition even when administered at suboptimal rates. These include effects on upper gastrointestinal microflora, splanchnic blood flow and modulation of immune responses, and such factors have led some to advocate early enteral nutrition, especially for patients with trauma or burns. However, the evidence to date in support of this practice is equivocal³. Furthermore, these putative benefits of enteral nutrition may be offset by complications relating to delivery systems. The increasing popularity of invasive methods of enteral feeding, such as via percutaneous gastrostomies and jejunostomies, has been accompanied by a rise in serious complications⁴.

It is frequently stated that total parenteral nutrition (TPN) leads to mucosal atrophy and the assumption is made that this predisposes to bacterial translocation which may account for increased septic morbidity. While true in rodents, the evidence is less clear in humans. Bacterial

translocation does occur in surgical patients and is associated with an increase in septic morbidity⁵, but TPN has not been shown to be associated with any increase in bacterial translocation⁶. Furthermore, there is no evidence that short-term TPN in humans results in mucosal atrophy⁷. More importantly, both experimental and clinical studies suggest that neither mucosal atrophy nor change in intestinal permeability, the other frequently employed surrogate measure of barrier function, predispose to bacterial translocation^{8,9}. These findings suggest that egress between epithelial cells is not the only mechanism responsible for translocation.

Whatever the results of investigative studies, the most important endpoint in the enteral *versus* parenteral debate must be clinical outcome. It is often assumed that parenteral nutrition is associated with a higher incidence of septic complications and a number of studies have reported a higher incidence of sepsis in association with TPN. However, most of these involved patients with abdominal trauma, whose average age and overall prognosis are very different to those of the typical patient who requires parenteral support^{2,3,6}.

The results of studies comparing enteral with parenteral nutrition need to be interpreted with caution. First, they need to be considered in the context of overall morbidity. Even if septic morbidity is higher in patients with abdominal trauma receiving TPN, the question arises as to whether or not this might be offset by complications related to delivery systems or a significant incidence of inadequate nutritional support with enteral feeding. Second, it is inappropriate to draw conclusions from studies in which patients who could tolerate an oral intake were randomized to receive TPN; such patients probably do not require TPN in the first place. Third, in many published studies the TPN groups have received different nutritional intakes to enteral groups. This has led many reviewers to suggest that the association of TPN with an increased incidence of sepsis is, in reality, not due to the route of nutritional support but to the increased energy intake received and the associated hyperglycaemia, which is commoner in those receiving TPN¹⁰. In other words, these studies may simply reflect the detrimental effects of overfeeding. Furthermore, the potentially confounding effects of different protein and

energy intakes or the effects of specific substrates, such as glutamine or long-chain fatty acids which may have specific immunostimulatory or immunosuppressive effects, are often not taken into consideration. Finally, any conclusion that TPN is associated with an increased incidence of sepsis must be tempered by the overall results of the many published trials that have compared enteral nutrition with TPN. A recent review of 31 such studies concluded that there is no consistent evidence that enteral feeding is associated with improved clinical outcome compared with TPN⁶. It is worth emphasizing, however, that most of these trials were conducted on perioperative patients of whom only a minority were severely malnourished.

In summary, for perioperative patients there is insufficient evidence to conclude that enteral feeding provides any distinct advantage in terms of preservation of gut barrier function or the development of infectious complications, or of mortality or morbidity, over parenteral feeding when energy and nitrogen intakes are similar. The mode of delivery of nutritional support should be decided by intestinal tolerance. For many patients, particularly the critically ill, a combination of enteral and parenteral nutrition will be appropriate. As enteral intake increases parenteral intake can be reduced, or vice versa. The enteral *versus* parenteral debate has run its course: future research should concentrate on methods that combine both routes of delivery in an attempt to optimize nutritional care.

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What an editor wants or expects from authors

C. H. Organ Jr

Archives of Surgery, 1411 East 31st Street, Oakland, California 94602, USA

In an ideal world the editor finds gratification in reviewing the work of authors who demonstrate an appreciation for the responsibility and obligations of authorship with its professional and personal rewards. It is mutually beneficial to the editor and author if the latter is familiar with the guidelines issued initially by the International Conference of Medical Journal Editors in 1985¹ and the uniform requirements for manuscripts submitted to biomedical journals issued in 1997². We are what we write. The editor expects the author, before submitting a manuscript, to have read the journal's instructions for authors and to have implemented these instructions.

Specific attention should be directed to copyright requirements, the accuracy of references, a clear definition of author responsibility, titles, illustrations, legends and tables. The editor expects the author to be familiar with the elements of informed consent, full financial disclosure, patient references, animal experiment guidelines, Institutional Review Board requirements, photographic consent, and statistical review where and when required. Compliance with these details avoids format changes that lead to publication delay and an unnecessary taxation of the editor's patience.

Fundamental to what editors want and expect from authors is embodied in the structured abstract: a clearly stated hypothesis, design of the study, the setting, intervention studies, outcome measures, results and conclusions. Data extraction for quality and validity is the precursor to quantitative and qualitative results.

Authors should be aware of specific details that attract the attention of the editor when reviewing manuscripts. The author is expected to have participated sufficiently in the work to take full responsibility for its content. Although 'substantial contribution' has not been clearly defined and is a work in progress, editors want authors to be involved in one or more of the following areas: (1) conception, design, analysis and interpretation of the data; (2) drafting the manuscript or revising it critically for content; and (3) approving the published version of the manuscript³.

An increasing number of bibliometric studies in various fields confirm that as many as 30 per cent of published articles may be classified as duplication of previously

published articles (i.e. redundant or salami publication). Editors are sensitive and usually responsive to both duplication and duplicity. A simple rule editors expect from authors would be 'if it has been in print, and especially if it has been peer reviewed, it shouldn't be put in print again'⁴. In an era of electronic publishing and computers, authors should appreciate that editors can easily acquire a computer-generated database of their previous and current work.

What does the editor expect from the authors? Respect for the peer review process, prompt reply to enquiries from the editor and full financial disclosure. Journal editors want and look forward to reviewing manuscripts of reasonable length (not word without end, amen). To investigate and track down these elements of a manuscript, particularly if funded by the biomedical industry, is not what the editor needs or wants. The editor expects adherence to sound grammatical structure. This includes the avoidance of slang, the absence of dangling participles, split infinitives and parallelism. The editor expects authors to be sensitive to the current trends and responsibilities of authorship inflation.

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Editors expect authors to realize that affiliation agreements with surgical societies do not guarantee publication even though they are reviewed and selected by a programme committee. Editors appreciate that this is an initial review process only; the editor and the editorial board make the final decision. The editor wants each author to realize that the peer review process is the best we have to offer presently and that manuscripts are usually improved by this process. The editor expects authors to avoid overall indictments and subjective comments. Authors should realize that disagreements (even debates) between the author, reviewer and editor are healthy and usually produce an improved manuscript. The editor expects authors to refrain in their

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Editors have an immense responsibility and expect authors to believe (1) that their manuscripts will be reviewed fairly and with honest feedback, (2) the editor to be an

honest and objective adjudicator and (3) the editor to be equitable in the selection of reviewers.

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Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

5 Peer review

Definition

Peer reviewers are external experts chosen by editors to provide written opinions, with the aim of improving the study.

Working methods vary from journal to journal, but some use open procedures in which the name of the reviewer is disclosed, together with the full or 'edited' report.

Action

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- 5 Reviewers should provide speedy, accurate, courteous, unbiased and justifiable reports.
- 6 If reviewers suspect misconduct, they should write in confidence to the editor.
- 7 Journals should publish accurate descriptions of their peer review, selection, and appeals processes.
- 8 Journals should also provide regular audits of their acceptance rates and publication times.

Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

8 Duties of editors

Definition

Editors are the stewards of journals. They usually take over their journal from the previous editor(s) and always want to hand over the journal in good shape.

Most editors provide direction for the journal and build a strong management team.

They must consider and balance the interests of many constituents, including readers, authors, staff, owners, editorial board members, advertisers and the media.

Action

- 1 Editors' decisions to accept or reject a paper for publication should be based only on the paper's importance, originality, and clarity, and the study's relevance to the remit of the journal.
- 2 Studies that challenge previous work published in the journal should be given an especially sympathetic hearing.
- 3 Studies reporting negative results should not be excluded.
- 4 All original studies should be peer reviewed before publication, taking into full account possible bias due to related or conflicting interests.
- 5 Editors must treat all submitted papers as confidential.
- 6 When a published paper is subsequently found to contain major flaws, editors must accept responsibility for correcting the record prominently and promptly.

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Abdominal fluid collection after laparoscopic cholecystectomy

A middle-aged man who complained of abdominal pain and bloat for 3 days after a combined laparoscopic cholecystectomy and umbilical hernia repair develops a fistula through the umbilical wound. How should care proceed? Vivian McAlister of Halifax, Nova Scotia replies.

Abdominal fluid collections after cholecystectomy are more common than previously thought; up to 80 per cent of bile fistulas are relatively symptomless. Several features in a large series reported by Lee *et al.*¹ raise concerns. The vast majority of collections went undrained and 21 per cent of those patients developed serious complications. Early clinical signs did not distinguish patients who became critically ill from those who did not and a poor outcome was associated with delayed drainage. Therefore a high degree of suspicion is required. Any patient who fails to recover from the usual low-grade postcholecystectomy discomfort after 3 days should be advised to return for examination and this should include ultrasonography. A small quantity of fluid is common at the surgical site, but larger collections should be drained. Drainage is most commonly achieved using the ultrasonographically guided percutaneous approach with a fine trocar and catheter, but return to the operating room for repeat laparoscopy should be considered. In a patient who is critically sick, emergency room placement of a catheter into the abdomen via the epigastric port site may allow a quick diagnosis and a surprisingly swift recovery if the offending fluid is bile.

In the clinical dilemma posed here, diagnosis has been hastened by the development of a fistula. Two questions should be answered: what is the nature of the fluid and do predisposing factors for ascites exist? Postcholecystectomy abdominal fluid may be blood, intestinal content, bile, ascites or combinations of these. Intestinal injury may be difficult to diagnose. It may be associated with persistent postoperative free air and bubbling at the fistula, or signs may be limited to a high white cell count in the fluid that may grow multiple organisms in culture. Duodenal injuries leak clear bile that can be distinguished from a biliary injury by the presence of a very large amount of amylase in the fluid.

In the jaundiced patient, ascitic fluid will look bilious. A simple bedside test is to compare the abdominal fluid with the urine; if they are equally dark, the fluid is ascites. This may be confirmed by laboratory estimation of the bilirubin content of the fluid and the serum. If the abdominal collection contains bile, a well placed drain should be left *in situ* for a few days. Many biliary leaks seal spontaneously,

signalled by diminution of the effluent without recurrence of the intra-abdominal collection. No further therapy is required if the liver enzyme concentrations return to normal. Persistent leaks should be investigated by endoscopic cholangiography. The commonest site of leakage in the biliary tree with a normal contour is the cystic stump. Decompression of the bile duct by stent, nasobiliary tube or sphincterotomy usually permits resolution. A persistent biliary fistula without evident leakage in a normal looking cholangiogram may signify a severed right inferior hepatic duct. This may be verified with a sinogram, performed by instilling water-soluble contrast agent into the drainage catheter. Careful planning for repair of this and other major bile duct injuries is required so that the first operation is definitive; the level of injury is usually raised in those whose first repair fails.

Ascites is the commonest morbidity for patients with cirrhosis undergoing abdominal operations. It may be resistant to treatment and can precipitate liver failure. A tip off to the diagnosis of cirrhosis in the male patient presented in this Dilemma could be the presence of an umbilical hernia. In the non-cirrhotic adult population, umbilical hernia is more common in women. In men, the presence of an umbilical hernia often precedes the diagnosis of liver disease, and hernia repair, before treatment of the liver, usually fails. A history of risk factors for liver disease, preoperative laboratory data (low albumin, low platelet count), splenomegaly on ultrasonography or a cirrhotic appearance of the liver at laparoscopy will help confirm the suspicion. Although rarely followed, it is good practice to include a description of the liver in the operative note of all laparoscopies and of its texture at all laparotomies. The majority of cirrhotic patients are undiagnosed at the time of cholecystectomy. The liver transplantation team should be consulted before elective cholecystectomy in patients with known cirrhosis, to determine the impact of surgery on future care. Patients with Child class A and B disease tolerate laparoscopic cholecystectomy better than open surgery, but patients in class C do very poorly with either approach. Care must be taken in those with portal hypertension as the caput medusae is most prominent in the extraperitoneal space around the umbilicus. Recanalization of the left umbilical vein, easily visible with ultrasonography, is a marker of these troublesome veins. The open approach for the placement of the umbilical laparoscopic port should be employed.

Ascites induced by cholecystectomy in patients with cirrhosis should be treated with a combination of potas-

sium-sparing and thiazide diuretics. Large-volume paracentesis with albumin transfusion may be required to initiate control that can be maintained with the diuretics. In the patient with an ascitic fistula, diversion of the leak to a percutaneous drainage catheter at a fresh site will promote wound healing. Contamination of the ascites, with worsening of the patient's condition and possible exclusion from transplantation, is a risk of open drainage by fistula or tube. Care must be taken to avoid prerenal renal failure, especially in those with evidence of hepatorenal dysfunction. Resistant ascites will respond to the placement of a transjugular intrahepatic portosystemic shunt, but deterioration in liver function may also occur.

Consultation with the liver transplantation team is, again, appropriate.

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Lymphoedema following surgery for breast cancer

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Background: Lymphoedema is a common complication of breast cancer treatment, affecting approximately a quarter of patients. Those affected can have an uncomfortable, unsightly and sometimes functionally impaired limb prone to episodes of superficial infection. The aetiology, pathophysiology and management of these patients is poorly understood.

Methods: This is a systematic review of all published literature on lymphoedema following treatment for breast cancer, using the Medline and Cinahl databases with cross-referencing of major articles on the subject up to the end of 1999.

Results and conclusion: The aetiology and pathophysiology of lymphoedema in patients with breast cancer appear to be multifactorial and are still not fully understood. Although conservative treatment techniques can be very successful in controlling symptoms, they do not afford a cure. The place of surgical and pharmacological therapy remains unclear. Improved understanding of the pathophysiology may assist in reducing the incidence of this condition, or help to identify those at greatest risk, in whom early initiation of conservative treatment measures may prove effective.

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Introduction

In 1908, Handley described the morbidity associated with a brawny swelling of the arm in patients with carcinoma of the breast¹. Halsted, in 1921, described the same condition as a complication of radical mastectomy, referring to it as 'elephantiasis chirurgica'². Lymphoedema has been described as 'a progressive pathologic state or condition characterized by chronic inflammatory fibromatosis and hypertrophy of the hypodermal and dermal connective tissues'³. Although now rarely seen in untreated breast carcinoma, it remains a common and disabling complication of breast cancer treatment (*Fig. 1*). Those affected have an uncomfortable, unsightly and sometimes functionally impaired arm prone to repeated episodes of superficial infection. There exists the extremely rare but potentially fatal possibility of secondary lymphangiosarcoma (Stewart-Treves syndrome)⁴.

In the UK, around 26 000 new cases of breast cancer are diagnosed each year⁵. The majority of these patients will receive surgical treatment involving dissection of axillary lymph nodes. Axillary clearance, as commonly advocated, provides a guide to prognosis, assists in planning adjuvant systemic therapy and minimizes axillary recurrence⁶; there is emerging evidence to suggest an impact on survival⁷. A

degree of arm swelling in the early postoperative period is commonly observed and tends to settle spontaneously within a matter of weeks⁸. Lymphoedema may, however, develop months or years after this (an interval of over 20 years has been reported), with around 75 per cent of cases occurring in the first year after operation^{9,10}. Onset may be gradual, or rapid. Patients occasionally identify a precipitating factor, such as a minor infection following a cut or graze, or a greater than usual degree of exercise involving the arm¹¹. Venepuncture has also been cited in this context¹². In 15 per cent of patients, the appearance of oedema represents local tumour recurrence within the axilla¹³. The swelling is initially soft, pits on pressure and may reduce with elevation. With time and recurrent superficial infection the characteristic changes of the 'brawny' arm are seen; the oedema is now non-pitting and accompanied by skin changes. Occasionally this situation progresses to unmistakable 'elephantiasis'¹⁴. The International Society for Lymphology has produced a classification for lymphoedema¹⁵:

Grade I swelling pits on pressure; may reduce with elevation

Grade II firmer, non-pitting; skin changes, hair loss, alteration to nails

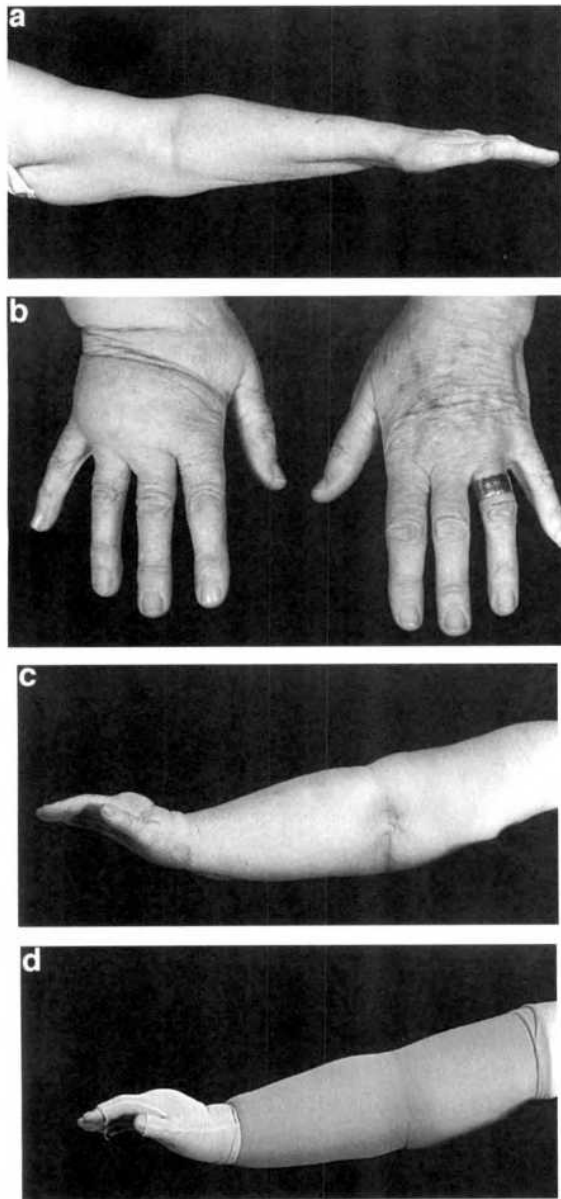


Fig. 1 Right arm volume excess of 63 per cent following breast cancer treatment:

- a Normal arm
- b Both hands
- c Affected arm
- d Compression sleeve and glove

Grade III elephantiasis; very thickened skin with huge folds

Prevalence

Quoted prevalence rates for lymphoedema vary. Much of this variation is due to different levels of awareness of the

problem, different techniques for measuring arm volume, and lack of a universal definition of what degree of swelling constitutes 'lymphoedema', as well as genuine differences resulting from variation in clinical practice. Kissin and colleagues¹⁶ reported a subjective prevalence of arm swelling, as noted by either patient or observer, of 14 per cent, but on measurement of volume excess compared with the contralateral arm, 25 per cent exceeded the 200-ml cut-off that had been adopted for this study. It should be noted, however, that the follow-up period in this study was variable: less than 5 years in 50 per cent of patients, 5–10 years in 30 per cent and more than 10 years in 20 per cent. Ivens *et al.*⁶ using the same objective definition, found a 24 per cent subjective prevalence of swelling against only 10 per cent on measurement. Britton and Nelson¹⁷ published a review of nine series published between 1908 and 1950, finding prevalence rates that ranged from 6.7 per cent¹⁸ to 62.5 per cent¹⁹. Hughes and Patel²⁰ assimilated 11 series published between 1940 and 1961, finding mean values for 'marked' swelling (volume excess greater than 750 ml) of 12.5 per cent, and for all swelling (volume excess greater than 150 ml) of 49.2 per cent. A majority of these patients had received treatment based on Halsted's radical mastectomy, with or without additional radiotherapy to the axilla. As more conservative surgical techniques were adopted, rates of lymphoedema fell, although great variation remained. In the 1960s and 1970s, larger series quoted figures ranging from 13 per cent²¹ to 57.5 per cent²², while rates as low as 2 per cent were claimed by some²³.

More recently, two large series on lymphoedema have been published. Schunemann and Willich²⁴ noted a lymphoedema rate of 24 per cent in a study of 5657 patients over an extended period. Similarly, Mortimer *et al.*²⁵ noted a lymphoedema rate of 28 per cent in 1249 patients with a mean follow-up of 9.5 years.

Clinical features

Although increase in size is the most obvious feature of lymphoedema, the physical and psychological morbidity associated with the condition must also be considered. Objective assessment of these variables is necessary when making the diagnosis and monitoring response to treatment.

Physical assessment

The most often quoted and comprehensible measure of the oedematous limb is increase in volume in comparison with the contralateral side. Altered circumference at set points along the arm provides a crude measure²⁶, while limb volume is now the accepted standard, with results expressed

as either a percentage increase or volume excess compared with the contralateral limb (more than 200 ml greater than the usual cut-off)^{6,16,24}. Initial measurements were performed using water displacement techniques, providing highly reproducible data²⁶. This method is messy and logistically impractical. Circumferential measurements along the limb, usually at 4-cm intervals, allow for subsequent volume calculation using equations for the volume of a cylinder or frustum (truncated cone). Repeated series show good correlation with water displacement data^{27–29}, although the circumferential measurement technique is unable to measure alteration in hand volume. Consideration should also be given to a variation of arm volume over the course of the day of up to 3 per cent, and the increased volume of the dominant arm, the mean value of which is in the region of 2 per cent^{27,30,31}.

Quoting results as a percentage change does not reflect the magnitude of the alterations that have occurred, as the compartments involved in the swelling (skin and subcutaneous tissue) constitute less than 20 per cent of total arm volume in the normal state²¹. Computed tomography³², magnetic resonance imaging^{33,34} and ultrasonography³⁵ allow for subtraction of the volume of the bony and muscular components to provide a more sensitive measure, but realistically only in a research context. The increased water content of the swollen tissues allows changes to be monitored using bioelectrical impedance^{36,37} and dual-beam absorptiometry techniques^{37,38}, which may have a useful role in monitoring response to treatment. Tonometry measures the deformation caused by a known force and provides a means of quantifying the pitting characteristics of the tissues^{39–41}.

Physical morbidity

The physical consequences of lymphoedema range from discomfort to life-threatening secondary tumours. Patients frequently complain that the affected limb feels heavy and less mobile^{42,43}, and performance of simple daily tasks such as dressing may be impaired⁴⁴. In two small studies, 37.5 per cent and 48 per cent of women complained of disabling pain^{9,43}. The affected limb is more susceptible to recurrent attacks of superficial infection, 'erysipelas', occurring to some degree in 53 per cent of patients in one series⁴⁵. This study also noted that, on examination, 77 per cent of the swollen arms displayed signs of subclinical infection, such as warmth, redness and increased induration. Although considered to be of bacterial origin, there is no microbiological evidence to support this.

In 1948, Stewart and Treves reported six cases of lymphangiosarcoma developing within lymphoedematous arms and eponymized the syndrome⁴. A 1996 review of the

literature revealed reports of 400 such cases⁴⁶, and a recently published population-based study from Sweden on 123 000 women with breast cancer reported 40 such sarcomas (suggesting a possible risk of this complication of around one in 1000)⁴⁷.

Psychological morbidity

A diagnosis of breast cancer is in itself a major psychological burden. Concerns about malignancy are added to by the more particular problems associated with surgery to the breast, affecting self-esteem and sexuality⁴⁸. Lymphoedema developing months or even years after the original operation is a further insult after the first hurdle has been cleared. Concern about the possibility of tumour recurrence may be added to by personal blame if, as is sometimes the case, the swelling develops after an episode of pronounced arm use⁴⁹. The discomfort, lack of mobility and reduced function of the affected limb all place a further strain on the patient, as does the cosmetic appearance of the swelling itself or the pressure sleeve prescribed to treat it, both of which may alter choice of clothing and cause avoidance of certain social situations⁹. Attempts to measure these psychological changes formally have been hampered by the apparent absence of a sufficiently sensitive tool, but do show consistently increased scores for patients with lymphoedema following treatment of breast cancer, compared with treated patients without arm swelling^{11,49–51}. Pain, poor social support, dominant hand involvement and avoidance-style coping mechanisms all seem to be predictors of a greater level of dysfunction⁵⁰. Surprisingly, none of the studies has shown a correlation between psychological morbidity score and extent of volume excess, suggesting that concentrating on volume reduction as the sole measure of response to treatment may be inappropriate.

Aetiology

The accepted aetiology for this condition is that dissection of the axilla interrupts the lymphatic drainage pathways from the arm, thus reducing the capacity for lymph drainage. The resulting inability to clear protein from the interstitial fluid leads to an increased protein concentration, with a reduction in the colloid osmotic pressure gradient which acts against capillary filtration. The volume of fluid leaving the capillaries therefore increases, with oedema developing until the increased hydrostatic pressure in the interstitium creates a new equilibrium, a 'high protein' oedema. The clinical observation that the subfascial compartment is not affected is presumably a result of

muscle contraction within this fixed-volume space, preventing fluid accumulation⁵².

The increased level of protein not only attracts fluid into the tissues, it also provokes inflammation and fibrosis within them⁵³, in time leading to the characteristic appearance of the brawny limb. The circulation of cellular elements such as lymphocytes and macrophages is hindered and their function may be suppressed⁵⁴. A reduction in cutaneous cell-mediated immunity has been demonstrated experimentally in lymphoedematous limbs, with impairment of both the afferent and efferent loops of the allergic contact immune response⁵⁵. Along with the attractive, protein-rich medium created, this accounts for the observed increase in susceptibility to infection. It may also explain the increased risk of malignancy associated with lymphoedema.

There remain, however, a number of questions regarding arm oedema following breast cancer surgery.

- 1 Why do some women develop this complication while others do not?
- 2 What explains the latent period preceding the onset of oedema?
- 3 Why is it that certain sections of the arm are 'spared'?
- 4 Why is it so difficult to create artificial models of lymphoedema in animals, employing far greater surgical trauma than that involved in breast cancer treatment?

Lymphatic physiology

The lymphatic system has two basic roles within the body. First, lymphoid tissue is involved in the production of cells and antibodies, destruction of red cells and other immunological tasks. Second, there is circulation of lymph, which serves to carry away from the tissues protein molecules and other large structures, including particulate matter⁵⁶. Water is also carried, but this is ostensibly as a solvent or vehicle for the larger molecules and has been estimated as totalling no more than 2–4 litres per day⁵⁷. Lymphatic vessels drain the interstitial fluid, which is itself derived from filtration⁵⁸ and diffusion⁵⁹ of water and molecules from the blood capillaries. The forces acting upon water in this exchange are the hydrostatic pressure gradient from capillary to interstitium, and the colloid osmotic pressure gradient exerted by the plasma proteins in the other direction. It has long been assumed that, while net flux of water is out into the interstitium from the arterial capillaries, in venous capillaries this is reversed. Recent work has, however, suggested that the mean venous pressure far exceeds net Starling pressure opposing capillary filtration (calculated from hydrostatic pressure of the interstitium and colloid osmotic pressure of both interstitium and plasma), such that net flux of water is always out of the capillary⁶⁰.

Oedema is defined as the accumulation of interstitial fluid in abnormally large amounts⁵⁷. This can occur as a result of one of a number of physiological changes: (a) an increase in filtration pressure caused either locally by arteriolar dilatation or venular constriction, or more globally by increased arterial inflow or elevated venous pressure; (b) a reduction in the osmotic pressure gradient resulting from either a decrease in plasma proteins or an increase in osmotically active material in the interstitium; (c) an increase in capillary permeability mediated by 'lymphagogues' such as substance P, histamines and kinins; and (d) a reduction in the flow of lymph.

The 'high protein' nature of lymphoedema was determined by a series of experiments in the 1950s in which fluid was aspirated from the subcutaneous compartment of swollen limbs using a fine needle^{61,62}. Comparison was made with fluid from 'low protein' oedemas, such as those associated with cardiac failure and nephrotic syndrome⁶². In patients with lymphoedema, there was some evidence that protein levels were higher in the more clinically severe cases, although this was not significant⁶¹. The most desirable comparison would have been with interstitial fluid from the unaffected contralateral limb, but sampling techniques at the time were unable to provide this. More recently, a study of women with postmastectomy oedema did make this comparison, sampling fluid by means of multifilamentous nylon 'wicks' under the skin and relying on capillary action⁶³. The results obtained revealed, most surprisingly, a reduced protein concentration in the interstitial fluid sampled from the swollen limb compared with that from the contralateral control, the difference apparently larger in cases of greater volume excess. These findings cast doubt on the idea of a primarily lymphatic aetiology for oedema following treatment of breast cancer.

Lymphatic anatomy

The small size of lymphatic vessels (no greater than 0.5 mm in the arm in normal conditions) makes their demonstration at cadaveric dissection difficult. With the added problem of multiple valves, injection casting is technically hard²¹. In the live subject, subcutaneous injection of india ink provides information about the superficial vessels, but not about deeper communications. There has been little to improve upon the anatomical descriptions of Rouviere, first published in 1932⁶⁴. Lymphatic capillaries in the connective tissue form a dense anastomotic plexus, draining into lymph-collecting vessels. These initially rely on external compression, principally secondary to striated muscle contraction, to generate flow, multiple valves ensuring unidirectional movement of lymph. In the larger, more proximal vessels, intrinsic smooth muscle within the vessel

wall generates waves of contraction, the magnitude of which is apparently determined by the supply of lymph, behaviour akin to the chronotropic and ionotropic actions of the heart⁶⁵. Superficial and deep systems are divided by the fascial layer, with little communication between the two.

In the arm, superficial drainage lymphatics from the hand and forearm converge to form radial, median and ulnar bundles. These come together above the elbow to create the medial upper arm bundle, which also receives drainage from the medial part of the upper arm. This bundle, in the form of three or four proximal trunks, pierces the clavipectoral fascia to enter the axilla⁶⁶. The lateral part of the upper arm drains via the smaller lateral upper arm bundle, while the deep system, carrying lymph from the muscular compartments, follows the brachial artery to the axilla. Rouviere described five groups of axillary nodes (axillary vein group, external mammary chain, scapular chain, central and subclavicular), now generally replaced by levels I–III. The deep lymphatic vessels and medial upper arm bundle drain into the central and axillary vein groups (levels I and II), with efferent vessels then passing to the subclavicular group (level III). From here, the subclavian lymphatic trunk emerges to drain into the venous system at the jugulo-subclavian confluence. The lateral upper arm bundle runs in the deltopectoral groove before draining directly into the subclavicular node group. In around 10 per cent of women this bundle terminates in the supraclavicular nodes, bypassing the axilla altogether^{64,67} (Fig. 2).

Using india ink injection to investigate ten autopsies and two amputated arms, Kubik⁶⁷ described two variants of the lateral upper arm bundle. In the 'long' variant, there is a direct connection between the radial bundle draining the forearm and the lateral upper arm bundle. Following axillary surgery and interruption of the drainage pathway of the medial upper arm bundle, lymph can pass to the lateral bundle via this communication and thence to residual level III nodes or to the supraclavicular node group. Women with this anatomical variant, it was proposed, are at low risk of developing lymphoedema, whereas those with the 'short' variant bundle, in whom no such communication exists, are at high risk. A similar theory was put forward by MacDonald¹⁹, who stated that the medial portion of the upper arm was the sole area draining exclusively to the axilla and so was most commonly affected by swelling. In clinical investigation of women with lymphoedema following breast cancer treatment, a number of lymphatic collaterals have been visualized: at the level of the axilla (Mascagni pathway), to the ipsilateral mammary chain or contralateral axilla, and through the chest wall⁶⁸.

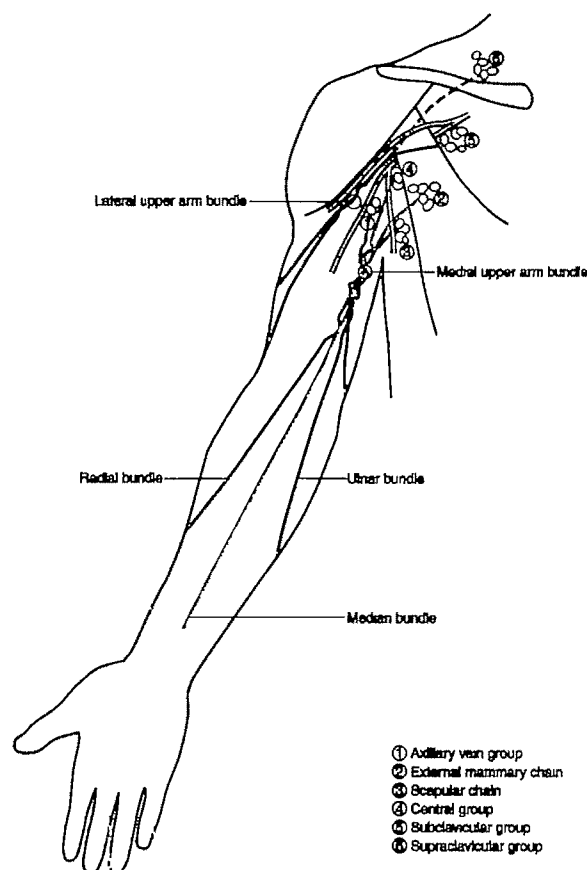


Fig. 2 Schematic representation of lymphatic drainage of the arm. The broken line indicates alternative drainage of the lateral collateral bundle to supraclavicular nodes

Associated factors

Many factors have been cited as increasing the risk of lymphoedema following treatment for breast cancer. Types of treatment, both surgery and radiotherapy, are the most consistent correlates and appear to account for the reduced incidence observed over the years. Support for this idea comes from a study of over 5000 women treated between 1972 and 1995, revealing a 39.5 per cent prevalence of arm swelling following radical mastectomy, 24.0 per cent after modified radical mastectomy and 9.3 per cent following breast-conserving surgery (although the axillary procedure was not specified for this group)²⁴. Another series demonstrated a 13 per cent incidence when an axillary procedure was performed and 4 per cent when it was not⁶⁹. Further analysis of the results showed a 37 per cent association with axillary clearance, 8 per cent with 'lower dissection' and 5 per cent with sampling. Kissin *et al.*¹⁶ found the prevalence of swelling following axillary sampling and irradiation to be equivalent to that following clearance of the axilla, and there

is general agreement that the combination of surgery and radiotherapy to the axilla is best avoided, with quoted prevalence rates more than double those for surgery alone^{16,24,69–72}.

Postoperative infection has often been put forward as a major correlative factor^{2,10}, and this may explain the apparent association with obesity^{70,71,73–75}, volume of postoperative drainage, duration of drainage and seroma formation¹⁰. As noted above, some women link the onset of their swelling with an episode of increased activity, which might suggest that oedema would be seen more commonly in the dominant arm. One study did find an 18 per cent prevalence for the dominant side compared with 2 per cent for the non-dominant⁶, but attempts to replicate this finding in a larger study failed to demonstrate any significant difference¹⁶. Other cited factors have included increasing patient age⁷³, advanced tumour stage¹⁶, nodal involvement⁷⁵, division of pectoralis minor during operation⁷³ and oblique skin incisions⁷¹; as many studies refute as support these associations.

Pathology

Information on the pathological changes underlying postoperative lymphoedema come from both animal and clinical studies.

Animal studies

The creation of animal models of lymphoedema has proved remarkably difficult. Ligation⁷⁶, transection and resection⁷⁷ of the lymphatic vessels draining the limb (following visualization of these with blue dye) leads to a transient oedema which usually resolves within 2–4 weeks. Lymphographic appearances during this time show an initial cessation of lymph flow at the point of intervention, followed by the development of an extensive mesh of collateral vessels which restore lymphatic drainage and coincide with the resolution of the oedema^{76,77}. It is unclear whether these collateral vessels are always present but not visualized, or develop in response to the trauma. Transected lymphatic trunks are seen to regenerate, with diminution of the collateral system, such that the lymphogram eventually returns to its preinterventional appearance. No such regeneration occurs following ligation or resection of the trunks, the collateral system remaining and enlarging. In cases in which wound infection develops, both clinical and radiographic resolution are delayed, and chronic states of lymphoedema have been observed⁷⁷. More recent work has found that the combination of surgical ablation and irradiation is the most reliable way of creating chronic oedema experimentally⁷⁸. It seems that the clinically

observed association between lymphoedema and both irradiation and wound infection is explained by extensive fibrosis preventing the formation of an adequate collateral lymphatic circulation.

Clinical studies

The majority of clinical studies have focused on investigation of the lymphatics, although a significant body of work now exists to suggest that there are other factors contributing to the aetiology of lymphoedema, with alterations noted in arterial inflow, venous return and plasma osmolality, as well as the intriguing possibility of the presence of lymphaticovenous communications.

Lymphatic studies

Clinical investigation of patients with lymphoedema was revolutionized by the introduction by Kinmonth in 1954 of direct lymphangiography⁷⁹. With a draining lymphatic visualized and dissected out following the subcutaneous injection of dye, direct cannulation enabled infusion of radio-opaque contrast agent and subsequent radiographic imaging. This demonstrated clearly a dilated lymphatic system distal to an axillary blockage, with varying degrees of collateral development. This is, however, a technically difficult procedure that is uncomfortable for the patient. It has been shown to damage the lymphatic vessels further⁸⁰ and is no longer in common use.

Indirect lymphoscintigraphy involves the subcutaneous injection of a solution of radiolabelled nanocolloid, with subsequent external scintillation detection in the region of the injection depot (initial uptake into lymphatics), in the extremity (transit in large collectors) and over regional lymph nodes (storage of colloid)⁸¹. Although the images are poorer than those obtained by direct lymphangiography, the indirect method has the advantage of also being a functional study that provides information on movement of protein within the lymphatic system. Commonly noted features in cases of lymphoedema include tracer flowing through the subdermis rather than lymphatic vessels (subdermal collateralization) and initial flow of tracer through lymphatics but then back into the subdermis upon reaching the site of obstruction (dermal backflow). Dermal backflow may be limited to only part of the arm, and the point of obstruction may be at the axilla or more distally, the phenomenon of 'die-back' referring to how this point may move distally with time⁸². Axillary and/or supraclavicular lymph nodes may or may not be visualized, depending on the extent of surgery performed and on individual anatomical variation⁶⁸. In a study of women who had undergone 'complete axillary clearance', nodal uptake could still be demonstrated in 60 per cent of cases following injection of colloid in the hand⁸³. In

all, 80 per cent of these nodes were in the axilla, with the remainder in the supraclavicular fossa and external mammary chain. In those in whom axillary clearance appeared to be complete, the incidence of lymphoedema was significantly greater. In a scintigraphic study of women with no evidence of lymphoedema 2 years after treatment for breast cancer, 50 per cent were shown to have impairment of lymphatic drainage⁸⁴. This might suggest that an impaired lymphatic system is able to keep up with demand, but that increase in demand, such as that provoked by exercise or infection leading to an increase in capillary filtration rate, overloads the system and leads to decompensation. This physiological basis of decompensation may be akin to that of a failing heart, with excessive load on the smooth muscle contractile system, or related to vessel dilatation leading to valvular incompetence.

Although the radiological techniques described above provide adequate information to confirm a diagnosis of lymphoedema, they are unable to quantify lymphatic flow rate. Initial attempts to quantify flow were based on studies of the rate of uptake of tracer by regional lymph nodes and proved more sensitive than subjective criteria alone in diagnosing lymphoedema⁸⁵. However, as a quantitative measure, the method is fundamentally flawed in that the lymph nodes themselves are not comparable with the contralateral side (and are not visualized at all if axillary clearance is complete) and because it measures velocity of lymph flow rather than flow rate. Flow rate is a function of velocity and cross-sectional area, and it is known that lymphatics are dilated in lymphoedema. Depot clearance studies examine the rate at which radiolabelled colloid is cleared from the initial site of injection, determined by local diffusion, ease of access to lymphatic vessels and flow rate^{86,87}. To improve comparability of data, patients should undergo a standardized exercise protocol following injection (such as repeated clenching and unclenching of the fist) to stimulate lymphatic flow^{81,85,88}.

Histological examination of proximal lymphatic trunks in cases of lymphoedema reveals destruction of endothelial and smooth muscle cells in the vessel wall, with or without obstruction of the lumen. One study suggested that, with the knowledge that intrinsic muscle contraction is a major stimulus to flow in these vessels, smooth muscle damage might reduce carrying capacity, even in the presence of a patent lumen³⁴. Might the return of smooth muscle function be a contributory factor in the resolution of early postoperative swelling?

Arterial studies

The frequently observed warmth of the swollen limb is usually ascribed to an element of subclinical infection, but it may also represent hyperaemia of non-infective origin. The

proposition that arterial inflow to the oedematous post-mastectomy limb may be increased was initially investigated using venous occlusion plethysmography²¹. Although huge variations in calculated flow rates were obtained, the suggestion was that arterial flow rate per unit volume of tissue was increased in the oedematous arm compared with the contralateral control. This was supported by the finding that the arteriovenous oxygen difference was reduced on this side, while radioisotope clearance studies showed the increased flow to be to skin and subcutaneous tissues but not to muscle. Doppler ultrasonographic techniques can be used to assess arterial flow by measuring mean blood velocity in the axillary artery and estimating the diameter of the vessel such that a cross-sectional area can be calculated⁸⁹. Again, variations in flow rates were found to be very large, but a pattern emerged of increased arterial inflow to the majority of arms following ipsilateral breast cancer surgery, more marked in cases in which lymphoedema had developed. One possible explanation for these findings may be loss of sympathetic tone, although a study testing sympathetically mediated vasoconstriction using inspiratory gasp and cool reflex provocation failed to demonstrate any impairment⁹⁰. Cutaneous revascularization in the swollen arm has been observed, although not of sufficient magnitude to explain any significant change in arterial flow⁹¹.

Venous studies

The role of altered venous dynamics in the aetiology of postmastectomy lymphoedema has long been debated. Veal, in 1938, using the relatively new technique of venography, claimed that 90 per cent of women with postmastectomy arm swelling had some abnormality of venous return⁹². Around the same time, however, a number of surgeons were routinely resecting a length of the axillary vein to ensure complete clearance of the axilla. Far from noting an increased incidence of arm swelling, a number claimed to have observed a reduction following adoption of this technique^{19,93,94}. In 1966, Hughes and Patel used lymphography and venography to investigate 19 women with postmastectomy oedema²⁰. While confirming that all had obstruction to lymphatic flow in the axilla, varying degrees of venous obstruction with collateral circulation around the shoulder were also observed. In all, 15 of these patients subsequently underwent surgical exploration of the axilla and in 12 it proved possible to free the vein from surrounding fibrosis. In these cases, postoperative reduction in arm volume was maintained at 2-year follow-up.

Recent developments in the field of Doppler ultrasonography have enabled non-invasive assessment of venous flow. Svensson and colleagues^{95,96} have outlined criteria showing direct evidence of altered venous return (intraluminal thrombus with absent flow, absent axillary or

subclavian vein, narrowed axillary or subclavian vein with immobility of walls during respiration, interruption of venous flow by abduction or rotation when the same did not occur in the contralateral arm) and indirect evidence (multiple draining veins around shoulder, loss of normal phasic flow pattern, loss of phasic movement of vein walls). In a study including 81 women with postmastectomy oedema, no abnormality was noted in any of the controls or contralateral arms. Only 30 per cent of swollen arms showed features of entirely normal venous return⁹⁷. Similar figures have been produced by other studies using Doppler ultrasonography⁹⁸, while others have reported an incidence of venous abnormality as low as 4 per cent⁹⁹. Recent use of magnetic resonance imaging has demonstrated a 40 per cent incidence of venous abnormality (either occlusion of the vein or narrowing with visible collateral development)⁹⁹, and this with the arm restricted to a single position and no assessment of flow pattern. The patients in this study subsequently underwent percutaneous transluminal balloon venoplasty, with or without stenting. Long-term results are not yet available.

Plasma osmolality

Plasma colloid osmotic pressure is a contributory factor to the Starling forces that determine capillary filtration, and is related ostensibly to plasma protein levels. In a study involving 51 patients with arm oedema following breast cancer treatment, significantly lower levels of plasma protein were observed in the study group compared with case-matched controls⁶³. This difference related mainly to the albumin fraction, although no levels outside the normal range were recorded. There was no difference in the use of tamoxifen, with its known albumin-lowering effect⁶⁰, between the two groups.

Lymphaticovenous communications

There is much evidence for the existence of communications between the lymphatic and venous systems other than drainage of the thoracic duct into the left subclavian vein^{100–103}. Most of this relates to studies in the abdomen, with particularly dense communications noted in the region of the left renal vein; the exact nature of the communication remains unclear. Such links are not surprising in view of the shared embryological origins, lymphatic vessels growing from veins as endothelial sprouts¹⁰². It is possible that these communications are non-functional in the normal situation, but open following the increase in lymphatic pressure created by proximal obstruction (pressure as high as 50 mmHg may be recorded in the thoracic duct)¹⁰⁴. Supporting data for this idea come from an experimental model in dogs, in which radioisotopic evidence for a direct communication has been observed in conjunction with

absence of the normal lymphographic response to proximal lymphatic obstruction (collateral circulation and dermal backflow)⁷⁶.

Aboul-Enein and colleagues¹⁰⁵ investigated 20 women with arm swelling after surgery for breast cancer, 20 with no swelling following similar treatment and 10 healthy controls. Radiolabelled human serum albumin was injected under pressure into an isolated distal lymphatic and serial blood samples were taken from the ipsilateral basilic vein; the hypothesis was that radioisotope activity in the venous blood would appear much earlier if patent lymphaticovenous communications were present. The result showed clear evidence of such communications in the group of women with no arm swelling following breast cancer treatment, but none in the lymphoedema or control groups. The conclusions drawn were that the presence or absence of potential lymphaticovenous communications in the arm was a principal factor in determining which patients were at risk of developing lymphoedema.

Treatment

Treatment strategies for lymphoedema fall into three main groups: conservative measures, drug treatment and surgery. At present, conservative measures form the mainstay of management, with surgery reserved for resistant cases (if at all). The place of pharmacological therapy is still unclear. The extent of treatment on offer varies greatly from centre to centre within the UK, and even more so between countries. The absence of an accepted 'gold standard' treatment leaves a definite place for the use of 'complementary' techniques in the management of this condition.

Conservative measures

The principles of conservative treatment of lymphoedema remain unchanged from the middle of the nineteenth century^{106,107}, with attention to the areas of hygiene, massage, compression, and remedial exercises.

Hygiene

This involves meticulous attention to skin care, control of fungal infection and thorough antisepsis following abrasions or minor wounds. Antibiotics should be started promptly at the first sign of cellulitis, or long-term prophylaxis considered.

Massage

Initially performed by a trained therapist, in time this can be taken over by a spouse or by the patient. Vigorous massage increases blood flow and can exacerbate the problem⁶⁵; only gentle manipulation is required to activate lymph flow alone.

A particularly rigorous variation on this theme, 'manual lymphatic drainage', is based upon work performed by Vodder¹⁰⁸. Starting with the premise that the axilla receives lymphatic drainage not only from the arm but also from the adjoining quadrant of the trunk, initiating massage in the arm is avoided as this may only displace fluid into another region with compromised lymphatic drainage. Vodder also feared that sudden displacement of lymphatic fluid into a previously unaffected area might overload the system and create iatrogenic oedema, and so his initial focus is on the unaffected adjoining quadrants, stimulating lymph flow and 'preparing the ground' for the greater volume of fluid to come. The massage moves gradually towards and then along the limb, always moving fluid towards an area already 'cleared'. About an hour is required for full attention to one limb.

Compression bandaging

One of the effects of lymphoedema is a reduction in the elastic properties of the tissue. Following reduction in arm volume by massage, there is very little mechanical resistance to the reaccumulation of fluid. The limb should therefore be bandaged immediately after a massage session to protect the advances made¹⁰⁹. Following completion of an intensive course of therapy, usually lasting 4 weeks, the patient is fitted with a graduated compression sleeve, which is worn most of the time, day and night (*Fig. 1d*).

Exercise

The role of exercise is based on the fact that flow along valved lymphatic vessels is stimulated by contraction of adjacent striated muscle. Compression garments should be worn while exercising to maximize the effect of muscle contraction. There is a concern that excessive exercise may increase blood flow into the limb, possibly exacerbating the problem. Dynamic muscle exercise (isotonic) is therefore preferred to static exercise (isometric) such as gripping⁶⁵.

Foldi is generally regarded as the originator of modern thinking on conservative management of lymphoedema, assimilating these ideas into his 'complex decongestive therapy'¹⁴. This involves an intensive course of treatment, 5 or 6 days a week for 4 weeks, by the end of which the patient should be well versed in ongoing self-management. Excellent results have been obtained by employing this technique¹¹⁰. In a study of 200 patients from Australia, arm volume expressed as a percentage of the contralateral limb decreased from a mean of 121 per cent to 107 per cent in grade I swelling after a 4-week course of treatment, and from 153 to 123 per cent for grade II swelling¹¹¹. Over the following year, with continued use of pressure garments and exercise, a further small reduction was observed. A second course of therapy, when required, had equivalent results.

Pneumatic compression devices have been advocated as an alternative to massage therapy and have formed the mainstay of therapy in the United States for some years. A variety of models are available, which can basically be divided into single- and multiple-chamber design. The multiple-chamber devices inflate sequentially from distal to proximal, theoretically pushing the fluid ahead of their inflation. This, however, is in direct contradiction to the teaching of Vodder¹⁰⁸. Very little in the way of comparative data for the efficacy of each method exists and there is no consensus regarding optimum pumping pressures, length and frequency of sessions, and ongoing treatment requirements. One study demonstrated significant improvement with a multiple-chamber device in patients with leg lymphoedema in whom a single-chamber device had failed previously¹¹². In a further study on 20 women with postmastectomy arm oedema, single chamber and manual drainage produced significantly better results than the multiple-chamber technique¹¹³. Potential drawbacks have been noted to include pain from the treatment itself and precipitation of entrapment neuropathies¹¹⁴. Simple elevation has, not surprisingly, been shown to be of no benefit on its own¹¹⁵. Aromatherapy massage has been put forward as a way of combining therapeutic massage and a positive experience for the patient¹¹⁶.

Pharmacological therapy

The use of drugs in the treatment of lymphoedema centres on attempts to encourage the breakdown of proteins deposited within a brawny limb. Autologous lymphocytes, extracted from the patient's blood, may be used to promote cytokine release by lymphocytes that in turn activates macrophage proteinases¹¹⁷. The benzopyrone group of agents, including coumarin, is thought to activate proteolysis by macrophages, and to induce an increase in total macrophage numbers¹¹⁴. Ease of administration is an obvious benefit over the autologous lymphocyte method, as benzopyrones can be given in tablet form or even applied topically (although with a depth of penetration of 1–2 cm this is of limited use)¹¹⁸. Two randomized placebo-controlled crossover studies have shown a significant benefit when treatment is given for several months^{119,120}. Response is slower than with physical therapy, with a reported reduction in volume excess of 50 per cent in 6 months. Not all studies have reproduced this benefit¹²¹ and, although early side-effects are limited, there is mild gastrointestinal upset in 2–5 per cent of patients¹¹⁸ and some concern about hepatotoxicity with prolonged use¹²². Benzopyrones are not, at present, licensed for this use in the UK. The perceived future role for these agents is as an alternative to physical therapy in situations where this is not

viable, or as an adjunct to physical therapy. An initial course of drug treatment may soften the limb, thereby improving response to subsequent physical measures. There is no place for the use of diuretics in the treatment of lymphoedema; these drugs may even exacerbate the problem by increasing the protein concentration in the interstitium, thus enhancing the stimulus to inflammation and fibrosis.

Surgery

Surgery for lymphoedema is usually reserved for cases resistant to conservative measures. The great variety of techniques cited in the literature bears testament to the absence of a single, obviously superior method. In general, operations may be divided into two groups, namely debulking procedures and attempts to influence lymphatic drainage.

Debulking procedures involve surgical excision of the subcutaneous tissue, with or without removal of some of the overlying skin, with epithelial cover being obtained over the deep fascia. The Charles procedure was first described in 1912, and variations on it are still performed¹²³. Poor wound healing and infection commonly follow, and the cosmetic result can be very poor. Since the underlying pathology remains, the swelling may return, often with a bizarre distribution resulting from extensive scarring and occasionally accompanied by large papillomas¹¹¹. More recently, liposuction through numerous stab incisions has been advocated, initially with moderately successful results^{124–127}. In a recent paper from Sweden, however, the authors claimed complete resolution of swellings up to a volume excess of 2500 ml, with a partial effect above this¹²⁸. The improvement was maintained at 12-month follow-up. The procedure is invasive and 28 per cent of patients require blood transfusion, but the initial results are promising.

In 1908, Handley described his technique of 'lymphangioplasty', running silk threads subcutaneously from the arm to the chest wall to provide a conduit for lymphatic drainage¹. The procedure was abandoned as postoperative infection and spontaneous extrusion of the implanted foreign material commonly occurred. Rubber tubes¹²⁹, nylon thread^{130,131} and fine polythene tubes¹³² have all been used with early success, but poor results on long-term follow-up. Further attempts to encourage lymphatic drainage have involved the use of tube pedicles to carry tissue fluid to the chest wall^{133,134} and buried dermis flaps to divert lymphatic drainage via the deep lymphatics¹³⁵. The latter technique was based on the observation that the muscular compartment is clinically unaffected in cases of lymphoedema. This is difficult to explain anatomically, as the deep lymphatics of the arm drain into the same axillary nodes as do the vessels of the superficial drainage system⁶⁴.

The technique, however, is claimed to yield a good clinical result in 61 per cent of cases at up to 5 years' follow-up; this is supported by clearance studies using radiolabelled albumin.

In 1962, Cockett and Goodwin¹³⁶ described the anastomosis of a dilated lumbar lymphatic to the spermatic vein to treat a case of chyluria. Subsequent development of microsurgical techniques has enabled lymphaticovenous anastomosis to emerge as a potential treatment of arm lymphoedema. Methods have been described with anastomosis between lymph node or dilated vessel and vein¹¹⁴, and a recent publication suggests that a pedicle of external connective adventitial and adipose tissue containing lymphatics can be roughly implanted into a small vein without the need for precise suture placement¹³⁷. Further variations have included a Teflon (Du Pont, Stevenage, UK) stent to support the anastomosis¹³⁸. Many studies have now shown good relief in 50–77 per cent of patients^{35,139–144}, although most report some eventual recurrence of the swelling, presumably as patency of the anastomosis is lost¹⁴⁰. Finally, one study demonstrated improved results when lymphaticovenous anastomosis was combined with a debulking procedure, compared with anastomosis alone¹⁴¹.

Future work

At present, lymphoedema following surgery for breast cancer remains a poorly understood and incurable problem. Present conservative treatment measures are aimed at minimizing morbidity without tackling the underlying pathology. Good results can be obtained and the possible contribution of pharmacological agents warrants further evaluation. Surgical lymphaticovenous anastomosis can restore lymphatic drainage, at least in the short term, and it may be that the best results are obtained when this is combined with a minimally invasive debulking procedure. Lack of awareness of the problem, and of resources to deal with it, remains a major limiting factor in management.

With cure an unrealistic possibility at present, emphasis should be placed on prevention and, for this, an improved understanding of the multifactorial aetiology of the condition is required. Might it be possible to identify preoperative factors that distinguish women at greatest risk of developing lymphoedema, and alter the proposed management of the axilla without compromising the principles of cancer treatment? Certainly the technique of sentinel lymph node biopsy offers the potential of greatly reducing the incidence of this problem by avoiding unnecessary axillary clearance in up to 50 per cent of patients¹⁴⁵. It may also be that postoperative changes, demonstrated in the latent phase before the development of swelling, might identify those in whom lymphoedema is most likely to occur. Early prophylaxis

lactic initiation of conservative treatment measures may then prove more effective than their institution when swelling has become established.

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Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review

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Background: Liver resection for colorectal metastases is the only known treatment associated with long-term survival; extrahepatic disease is usually considered a contraindication to such treatment. However, some surgeons do not regard spread to the hepatic lymph nodes as a contraindication provided that these nodes can be excised adequately. A systematic review of the literature was undertaken to address this issue.

Methods: An electronic search using Medline, Cancerlit and Embase databases was performed for studies reporting liver resection for colorectal metastases from 1964 to 1999. Data were extracted from papers reporting outcome for patients with positive hepatic nodes and analysed according to predetermined criteria.

Results: Fifteen studies were identified that gave survival data on 145 node-positive patients. Five patients were reported to have survived 5 years after liver resection; one was disease free, two had recurrent disease and the disease status was not described in the remaining two. Five studies containing 83 patients specified a formal lymph node dissection as part of the surgical procedure and four of the five node-positive 5-year survivors were from these studies.

Conclusion: There are few 5-year survivors after liver resection, with or without lymph node dissection, for colorectal hepatic metastases involving the hepatic lymph nodes.

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Introduction

Liver resection for colorectal metastases is standard treatment for patients in whom all disease can be excised. Five-year survival ranging from 20 to 51 per cent is reported (Table 1) and the majority of 5-year survivors are still alive after 10 years¹. The presence of extrahepatic disease at the time of liver resection imparts a dismal prognosis^{2–6}. Most surgeons regard metastases to the hepatic lymph nodes as extrahepatic disease⁷ and would not proceed with liver resection in such circumstances. However, it is known in primary colorectal cancer with regional node involvement that surgery can still result in long-term survival. If the same were true for colorectal liver metastases then simultaneous liver resection and hepatic node dissection should result in long-term disease-free survival for a proportion of patients who have positive hepatic nodes. Several recent studies have suggested that liver resection may not be contraindicated in such cases^{8–10}. The purpose of the present article is to review the literature systematically to determine if there is evidence to support this hypothesis.

Methods

An electronic search was undertaken of the Medline, Embase and Cancerlit databases from 1964 to 1999. The search terms *hepatic resection* or *liver resection*, and *colorectal* or *colon* or *rectal*, and *metastasis* or *metastases* were used. These terms were mapped to Medline Subject Headings (MESH) terms as well as being searched for as text items. All papers identified and published in the English language were obtained. In addition, the reference lists in each paper were crosschecked manually for further relevant papers.

The following criteria were used to select patients from studies identified for inclusion in the analysis: liver resection was undertaken for colorectal metastases, metastases were found in the hepatic lymph nodes, survival data were reported for patients with positive nodes, the publication date was on or after 1960, and the paper was written in English. Studies of repeat hepatic resection or combined resections of hepatic and pulmonary disease were excluded.

Each paper meeting the criteria was analysed with a standard pro forma. The information obtained included the

Table 1 Studies of hepatic resection for colorectal metastases and reason for exclusion from analysis

Reference	Year	No. of patients*	Overall survival	Reason for exclusion from analysis
Adson ³⁵	1979	60	22% 5-year	NSND; some of the patients in a subsequent study ³⁵
Adson and Van Heerden ³⁶	1980	34	32% 3-year	NSND
Adson <i>et al.</i> ³⁷	1984	141	25% 5-year	NSND
Almersjo <i>et al.</i> ³⁸	1976	14	31% 2-year (excluding 1 postop. death)	NSND
Attiyeh <i>et al.</i> ³⁹	1978	25	40% 5-year	NSND
Attiyeh and Wichern ⁴⁰	1988	20	35% 5-year actuarial	NSND
Augelli <i>et al.</i> ⁴¹	1988	18	44% 2-year actuarial	NSND
August <i>et al.</i> ⁴²	1985	51	Not reported	7 node-positive patients not resected
August <i>et al.</i> ¹²	1985	33	53% 4-year estimated	NSND
Bengmark <i>et al.</i> ⁴³	1982	39	11 survivors, 3 had reached 5 years	NSND
Bismuth <i>et al.</i> ⁴⁴	1988	43	33% 3-year actuarial	NSND
Blumgart <i>et al.</i> ⁴⁵	1979	6	Survival data not reported	Survival data not reported; NSND
Boey <i>et al.</i> ⁴⁶	1981	7	Actuarial survival not reported	NSND
Bozzetti <i>et al.</i> ⁴⁷	1987	45	37% 5-year actuarial	NSND; may be the same patients in a subsequent paper ⁴⁸
Bozzetti <i>et al.</i> ⁴⁸	1988	45	29% 5-year actuarial	NSND
Bozzetti <i>et al.</i> ⁴⁹	1992	229	Survival data not reported	Survival data not reported; NSND
Bozzetti <i>et al.</i> ⁵⁰	1993	39	47% at 36 months	NSND
Bradpiece <i>et al.</i> ⁵¹	1987	24	44% 3-year actuarial	NSND
Brasfield <i>et al.</i> ⁵²	1972	50 liver resections; no. of colorectal metastases not specified	—	No. of colorectal metastasis cases not specified
Brunschwig ⁵³	1963	11	Not reported	NSND
Butler <i>et al.</i> ⁵⁴	1986	62	34% 5-year	NSND
Cady <i>et al.</i> ⁵⁵	1979	4	1 survivor at 3 years	NSND
Cady and McDermott ⁵⁶	1985	23	15 with major resection and ≤3 lesions 40% 5-year; 5 with >3 lesions 0% 5-year	NSND
Cady <i>et al.</i> ⁵⁷	1998	244	20% 5-year actuarial (estimated from graph)	NSND
Cobourn <i>et al.</i> ⁵⁸	1987	41	25% 5-year actuarial	NSND
Cole and Ferguson ⁵⁹	1992	43	Survival data not reported	Survival not reported
Coppa <i>et al.</i> ⁶⁰	1985	25	25% 5-year	NSND; data in a subsequent paper ⁶¹
Coppa ⁶¹	1990	42	22% 5-year	NSND
Cregan <i>et al.</i> ⁶²	1986	7	Actuarial survival not reported	NSND
Dillard <i>et al.</i> ⁶³	1969	8	25% 5-year	Cancer type not specified
Doci <i>et al.</i> ⁶⁴	1991	100	30% 5-year	NSND
Doci <i>et al.</i> ⁶⁵	1995	208	Not reported	NSND; survival not reported. Some patients included in previous paper ⁶⁴
Ekberg <i>et al.</i> ⁶⁶	1986	44	3 survivors at 5 years	Data in a subsequent paper ⁶⁷
Ekberg <i>et al.</i> ⁶⁷	1986	72	16% 5-year	NSND
Ekberg <i>et al.</i> ⁶⁸	1987	68; 6 node positive	Actuarial survival not reported	Data in a subsequent paper ⁶⁶
El-Domeir ⁶⁹	1980	2	0% 5-year	NSND
Elias <i>et al.</i> ¹³	1996	100; 14 node positive	Survival data not reported	Survival data not reported
Elias <i>et al.</i> ⁷⁰	1998	187	25% 5-year actuarial	NSND
Elias <i>et al.</i> ⁷¹	1998	136	28% 5-year actuarial	NSND
Fegiz <i>et al.</i> ⁷²	1985	28	Actuarial survival not reported	NSND
Fegiz <i>et al.</i> ⁷³	1991	47	12% 5-year for stage I	NSND
Fegiz <i>et al.</i> ⁷⁴	1991	212	24% 5-year actuarial (estimated from graph)	NSND
Finch <i>et al.</i> ⁷⁵	1998	50	65% 3-year actuarial	NSND
Flannagan and Foster ⁷⁶	1967	45	23% 5-year	NSND

Table 1 Continued

Reference	Year	No. of patients*	Overall survival	Reason for exclusion from analysis
Fong <i>et al.</i> ⁷⁷	1995	128	35% 5-year actuarial	NSND
Fong <i>et al.</i> ⁷⁸	1997	456	38% 5-year actuarial	Data in a subsequent paper ¹⁴
Fong <i>et al.</i> ¹⁴	1999	1001; 10 node positive	37% 5-year actuarial; node-positive patients included with other extrahepatic disease with a 5-year survival of 18%	Survival of node-positive patients unclear
Fortner <i>et al.</i> ⁷⁹	1978	17	72% 3-year actuarial	NSND
Fortner <i>et al.</i> ⁸⁰	1981	43	71% 3-year	Node positive patients combined with other tumour types in the analysis
Fortner <i>et al.</i> ⁸¹	1984	65	57% 3-year actuarial	NSND
Fortner ⁸²	1988	77	49% 5-year actuarial	NSND
Foster <i>et al.</i> ⁸³	1968	3	None over 2 years	NSND
Foster ⁵	1978	2	Included in multicentre analysis	Survival data not reported
Fowler <i>et al.</i> ⁸⁴	1992	11	Actuarial survival not reported	NSND
Franco <i>et al.</i> ⁸⁵	1988	4	All alive at 6–24 months' follow-up	NSND
Franco <i>et al.</i> ⁸⁶	1989	28	Not reported	Survival data not reported
Friesen <i>et al.</i> ⁸⁷	1967	3	Alive at 18 months, 3 years and 14 years	NSND
Fuhrman <i>et al.</i> ¹⁵	1995	107; 16 node positive	44% 5-year actuarial	Node-positive patients not resected
Gazzaniga <i>et al.</i> ⁸⁸	1991	66	25% 5-year actuarial	NSND
Gayowski <i>et al.</i> ⁸⁹	1994	204; 6 node positive	32% 5-year actuarial	Data in a subsequent paper ²³
Gennari <i>et al.</i> ⁹⁰	1986	48	53% 3-year	Data in a subsequent paper
Habib <i>et al.</i> ⁹¹	1993	17	Survival data not reported	Survival data not reported
Hananel <i>et al.</i> ⁹²	1995	26	30.5% 5-year actuarial	NSND
Hanks <i>et al.</i> ⁹³	1980	7	Not calculated for the colorectal cases	NSND, ?data in a subsequent paper ⁹⁴
Hardy <i>et al.</i> ⁹⁵	1998	52	55% 5-year actuarial for Dukes A and B; 12% for Dukes C	NSND
Harmon <i>et al.</i> ⁹⁶	1999	110	46% 5-year actuarial	NSND
Hodgson <i>et al.</i> ⁹⁷	1992	22	35% 5-year actuarial	NSND
Hohenberger <i>et al.</i> ⁹⁸	1994	141	20% 5-year actuarial	Those with positive nodes excluded
Holm <i>et al.</i> ⁹⁹	1989	35	Actuarial survival not reported; 31% alive at 3 years or more	NSND
Hu <i>et al.</i> ¹⁰⁰	1994	26	41% 2-year actuarial	NSND
Hughes <i>et al.</i> ¹⁰¹	1969	3	2 alive at 2 and 10 months; 1 dead at 12 months	NSND
Hughes <i>et al.</i> ¹⁰²	1986	607	33% 5-year actuarial	Data in a subsequent paper ²⁰
Hughes <i>et al.</i> ¹⁰³	1988	100 5-year survivors	—	Data in a subsequent paper ²⁰
Hughes <i>et al.</i> ¹⁰⁴	1988	859	33% 5-year actuarial	Data in a subsequent paper ²⁰
Irie <i>et al.</i> ¹⁰⁵	1999	79	24% 5-year actuarial	NSND
Isenberg <i>et al.</i> ¹⁰⁶	1996	17	47% 5-year actuarial	NSND
Iwatsuki <i>et al.</i> ¹⁰⁷	1983	24	40% 5-year actuarial	NSND
Iwatsuki <i>et al.</i> ¹⁰⁸	1986	60	45% 5-year actuarial	Data in a subsequent paper ¹⁰⁹
Iwatsuki <i>et al.</i> ¹⁰⁹	1988	90	36% 5-year	NSND
Jaeck <i>et al.</i> ¹¹⁰	1997	1818	26% 5-year actuarial	NSND
Jarnagin <i>et al.</i> ¹¹¹	1999	329	Not reported	Data in a subsequent paper ¹⁴
Jatzko <i>et al.</i> ¹¹²	1995	66	30% 5-year	NSND
Jatzko <i>et al.</i> ¹¹³	1991	22	Actuarial survival not reported	NSND
Jenkins <i>et al.</i> ¹¹⁴	1997	131	25% 5-year actuarial	NSND
Jourdan <i>et al.</i> ¹¹⁵	1999	53	27%	NSND
Kambouris ¹¹⁶	1983	5	Survival not reported	NSND
Kawasaki <i>et al.</i> ¹¹⁷	1994	5	Actuarial survival not reported	NSND
Kemeny <i>et al.</i> ¹¹⁸	1985	14	Not reported	Data in a subsequent paper ¹⁶
Kemeny <i>et al.</i> ¹⁶	1986	18	Not reported	14 node-positive patients not resected
Keyserlingk <i>et al.</i> ¹¹⁹	1985	5	55% 5-year actuarial	NSND
Klompje <i>et al.</i> ¹²⁰	1987	20	7 survivors at 2 years	NSND
Kortz <i>et al.</i> ⁹⁴	1984	16	29% 5-year	NSND
Lee <i>et al.</i> ¹²¹	1993	18	58% 3-year actuarial	NSND

Table 1 Continued

Reference	Year	No. of patients*	Overall survival	Reason for exclusion from analysis
Lefor <i>et al.</i> ¹²²	1988	66 resections; 16 of 107 laparotomies with positive nodes	Not reported	Management of node-positive patients not specified
Lim and McPherson ¹²³	1983	8	1 survivor at 5 years	NSND
Lind <i>et al.</i> ¹²⁴	1992	50	28% 5-year actuarial	NSND
Lise <i>et al.</i> ¹²⁵	1990	39	32% 5-year actuarial	NSND
Lise <i>et al.</i> ¹²⁶	1991	64	32% 5-year actuarial	NSND
Little and Hollands ¹²⁷	1987	26	51% 5-year actuarial	
Localio <i>et al.</i> ¹⁹⁴	1976	1	Not reported	NSND
Logan <i>et al.</i> ¹²⁸	1982	19	63% 2-year	NSND
Lorenz <i>et al.</i> ¹²⁹	1998	91	35% 5-year actuarial (from survival curve)	NSND
Macphee ¹³⁰	1969	8	Not reported	Survival data not reported
Maddern <i>et al.</i> ¹³¹	1995	12	Long-term survival not reported	Long-term survival not reported
Marmorale <i>et al.</i> ¹³²	1996	73	27% 5-year actuarial	NSND
Minton <i>et al.</i> ¹³³	1989	98	4 survivors at 5 years, actuarial survival not calculated	NSND
Miyazaki <i>et al.</i> ¹³⁴	1999	168	27% 5-year survival if IVC not involved; 22% if IVC involved	NSND
Morrow <i>et al.</i> ¹³⁵	1982	29	27% 5-year	NSND
Muhe <i>et al.</i> ¹³⁶	1982	38; no. with colorectal metastases not stated	20% 5-year	NSND
Nadig <i>et al.</i> ¹³⁷	1997	275	26% 5-year actuarial	NSND
Nims ⁸	1984	9	2-years' follow-up with 1 dead	NSND
Nordlinger <i>et al.</i> ¹³⁸	1987	80	25% 5-year actuarial	NSND
Nordlinger <i>et al.</i> ¹³⁹	1996	1568	8% 5-year actuarial	NSND
Nuzzo <i>et al.</i> ¹⁴⁰	1997	58	17% 5-year actuarial	NSND
Olak <i>et al.</i> ¹⁹⁵	1986	25	50% 5-year actuarial	NSND
Ong and Lee ¹⁴¹	1975	3	Short-term survival only reported	Survival not reported, NSND
Peden and Blalock ¹⁴²	1963	1	Alive at 5 years	NSND
Petrelli <i>et al.</i> ¹⁴³	1985	36	45% 2-year	NSND
Petrelli <i>et al.</i> ¹⁴⁴	1991	62	Overall survival not specified	NSND
Pinson <i>et al.</i> ¹⁴⁵	1996	95	38% 5-year actuarial	NSND
Pommier <i>et al.</i> ¹⁴⁶	1987	25	Survival specific to colorectal metastases not reported	Survival specific to colorectal metastases not reported; NSND
Rajpal <i>et al.</i> ¹⁴	1982	34	Median survival 31 months at a mean of 23 months' follow-up	Data in a subsequent paper ¹⁴³
Rees <i>et al.</i> ¹⁴⁸	1997	89	37% 5-year actuarial	NSND
Rimar and Howells ¹⁴⁹	1984	11	33% 2-year actuarial	Data in a subsequent paper ⁴¹
Rosen <i>et al.</i> ¹⁵⁰	1992	280	25%	Data in a subsequent paper ²¹
Sarker <i>et al.</i> ¹⁵¹	1993	12	42% 3-year actuarial	NSND
Sato <i>et al.</i> ¹⁵²	1998	36	43% 5-year actuarial from time of colonic resection	NSND
Scheele <i>et al.</i> ¹⁵³	1990	226	40% 5-year actuarial (of the 173 with 'curative' resections who survived hospital)	Data in a subsequent paper ²¹
Scheele <i>et al.</i> ¹⁵⁴	1991	226	Not reported	Data in a subsequent paper ²¹
Scheele <i>et al.</i> ¹⁷	1995	434; 3 node positive	39% 5-year actuarial (excluding operative deaths)	No clear survival data for node-positive patients
Schlag <i>et al.</i> ¹⁵⁵	1990	122	~27% 5-year actuarial for metachronous metastases; ~10% 5-year actuarial for synchronous metastases (estimated from graph)	NSND
Scott <i>et al.</i> ¹⁵⁶	1995	49	58% 3-year actuarial	NSND
Seifert and Morris ¹⁵⁷	1998	44	Median overall survival 33 months	NSND
Sesto <i>et al.</i> ¹⁵⁸	1987	61	28% 5-year actuarial	NSND
Shirabe <i>et al.</i> ¹⁵⁹	1997	31	39% 5-year actuarial	NSND
Sitzmann <i>et al.</i> ¹⁶⁰	1994	52	Not reported	Survival data not reported

Table 1 Continued

Reference	Year	No. of patients*	Overall survival	Reason for exclusion from analysis
Starzl <i>et al.</i> ¹⁶¹	1980	3	Long-term survival not reported	NSND
Steele <i>et al.</i> ¹⁶²	1984	30	30% 5-year actuarial	NSND
Steele <i>et al.</i> ¹⁶³	1991	69	91% 1-year actuarial	NSND
Stehlin <i>et al.</i> ¹⁶⁴	1988	43	20% 5-year	NSND
Stephenson <i>et al.</i> ¹⁶⁵	1988	55	30% 5-year actuarial	NSND
Stimpson <i>et al.</i> ¹⁶⁶	1987	23	Not reported	Survival data not reported
Sugihara <i>et al.</i> ¹⁶⁶	1993	109	48% 5-year actuarial	NSND
Taylor <i>et al.</i> ¹⁶⁷	1983	16	42% 42-month survival	NSND
Thompson <i>et al.</i> ¹⁶⁷	1983	22	31% 5-year actuarial	NSND
Tomas-de-la-Vega <i>et al.</i> ¹⁶⁸	1984	38	33% 3-year survival for the 34 having only one operation	NSND
Tsao <i>et al.</i> ¹⁶⁹	1994	162	Not reported	Survival data not reported
Tsuzuki <i>et al.</i> ¹⁷⁰	1984	12	~42% 5-year actuarial (estimated from graph)	NSND
Turunen <i>et al.</i> ¹⁷¹	1986	12	41% 3-year actuarial	NSND
van Ooijen <i>et al.</i> ¹⁷²	1992	118	21% 5-year actuarial	NSND
Vassilopoulos <i>et al.</i> ¹⁷³	1981	6	Not reported	Survival data not reported; NSND
Vetto <i>et al.</i> ¹⁷⁴	1990	58	Not reported	Survival data not reported
Vogt <i>et al.</i> ¹⁷⁵	1991	36	20% 5-year actuarial	NSND
Wade <i>et al.</i> ¹⁷⁶	1996	161	26% 5-year actuarial	NSND
Wagman <i>et al.</i> ¹⁷⁷	1990	21	Overall survival not reported	NSND
Wagner <i>et al.</i> ¹⁷⁸	1984	141	25%	NSND
Wanebo <i>et al.</i> ¹⁷⁹	1978	29	28% 5-year disease-free survival	NSND
Wanebo <i>et al.</i> ¹⁸⁰	1996	74	24% year (excluding 5 60-day postop. deaths)	NSND
Wang <i>et al.</i> ¹⁸¹	1996	54	26% 5-year actuarial	NSND
Waterhouse ¹⁸²	1965	1	Survived 1 year	NSND
Wilson and Adson ¹⁸³	1976	60	28% 5-year	NSND
Woodington and Waugh ¹⁸⁴	1963	7	10 months to 9.5 years	NSND
Yamaguchi <i>et al.</i> ¹⁸⁵	1993	40	41% 5-year actuarial	NSND
Yamamoto <i>et al.</i> ¹⁸⁶	1995	40	Not reported	Survival data not reported
Yamamoto <i>et al.</i> ¹⁸⁷	1999	96	51% 5-year actuarial	NSND
Yasui <i>et al.</i> ¹⁸	1997	81; 11 node positive	Not reported	Survival data not reported for the node-positive patients
Younes <i>et al.</i> ¹⁸⁸	1991	116	75% 2-year	NSND
Zavadsky <i>et al.</i> ¹⁸⁹	1994	6	83% 3-year	NSND
Zieren <i>et al.</i> ¹⁹⁰	1993	90	31% 5-year actuarial	NSND
Zieren <i>et al.</i> ¹⁹¹	1994	18	25% 5-year actuarial	Data in an earlier paper ¹⁹⁰

*Resection with curative intent. NSND, node status not described; IVC, inferior vena cava

number of patients undergoing resection for colorectal liver metastases, the number with positive hepatic nodes, and 5-year survival data for the node-positive patients. The surgical details of the node dissection were also recorded, if provided, and authors were contacted for additional information as necessary. Information about whether the lymph node metastases were macroscopically or only microscopically evident was recorded when available. Care was taken to exclude repeated reports from the same institution. When this occurred only the most recent or most complete report was used.

Results

One hundred and eighty-five studies were identified describing liver resections for colorectal cancer. One

hundred and sixty-three did not describe the lymph node status of the patients or repeated data from other publications. Those studies, and the reasons for exclusion from further analysis, are summarized in Table 1. Also included in Table 1 are eight studies^{11–18} in which node-positive patients were identified but did not undergo resection (37 patients) or for whom survival data were not reported separately (42 patients). The remaining 15 studies describe 145 patients who underwent hepatic resection for colorectal metastases, were identified as having hepatic lymph node metastases and had survival data reported^{1,7,9–11,19–21,23–26,30,192,193}. The details of these studies are summarized in Table 2. Five of the 145 patients were reported as being alive at 5 years. One was apparently disease free, two were alive with recurrent disease and disease status was not given for the remaining two patients.

In ten of the 15 studies (62 patients) either no formal lymph node dissection was undertaken or the paper did not specify how the involved hepatic lymph nodes were dealt with at the time of liver resection. There was one 5-year survivor (disease free) among these 62 patients. In five of the 15 studies (83 patients) a formal hepatic lymph node dissection was undertaken at the time of liver resection^{9,10,19,20,30}. There were four 5-year survivors (two with recurrence and two disease status unknown) among these 83 patients. Therefore, the reported 5-year survival for node-positive patients with colorectal liver metastases undergoing liver resection and lymph node dissection was 5 per cent. This should be regarded as a minimum figure because follow-up was not complete to 5 years for all patients.

Only one of the 15 papers clearly specified whether the lymph node involvement was macroscopically or only microscopically evident⁹. In that study patients with macroscopic disease were excluded. All 35 patients, therefore, had microscopic lymph node involvement and underwent lymph node dissection; there were no 5-year survivors.

Discussion

Liver resection can result in long-term survival in selected patients with colorectal metastases but only 10–15 per cent of such patients are suitable for resection^{2–5,28} and it is important to identify those for whom surgery offers the best prospects. There has been some debate about whether disease in the hepatic lymph nodes should be regarded as a contraindication to resection in the same way as distant extrahepatic disease. In a retrospective series of 62 patients who were deemed not resectable at laparotomy, Gibbs *et al.*²⁹ found that in seven (11 per cent) portal or coeliac nodes were the only site of extrahepatic disease. It is not surprising that untreated hepatic node disease is associated with a poor prognosis. It is less clear whether treating this disease by combined excision of liver and hepatic lymph node metastases can improve the outcome. Of the 185 studies identified in this review, five gave outcome data on node-positive patients who underwent hepatic lymph node dissection in addition to liver resection.

The study by Nakamura *et al.*²² has often been quoted as justification for an aggressive surgical approach in node-positive patients³. They reported a 5-year survival rate of 40 per cent in those with positive hepatic nodes. However, this survival figure is an actuarial analysis of only six patients and excludes one in-hospital death. There were two survivors at 49 and 66 months, both of whom had undergone repeat hepatectomy for recurrence and both of whom had further recurrence at the time of reporting. A recent update on this study in 1999³⁰ indicated that there were two node-positive

5-year survivors of 79 resections carried out over 20 years. Two other Japanese groups have described their experience with routine hepatic lymph node dissection in patients undergoing resection for colorectal liver metastases^{10,19}. Of 16 node-positive patients only one was reported to be alive at 5 years.

The Registry of Hepatic Metastases described 25 node-positive patients who underwent combined liver resection and lymph node dissection²⁰. It is possible that the registry data repeat some data already presented in other studies. However, there was only one 5-year survivor in this group. The node-positive patients in fact had a poorer survival than the 37 patients with more distant extrahepatic disease excised at the time of liver resection (who had a 20 per cent overall and 4 per cent disease-free 5-year survival).

Beckhurts *et al.*⁹ undertook a prospective study of 126 patients in whom routine lymph node dissection was undertaken. Those with macroscopically evident lymph node metastases were not included. Their technique involved removal of Japanese Gastric Cancer Study Group areas 12 and 13 (K. Beckhurts, personal communication) and 35 patients (28 per cent) were found to have histologically positive nodes. None of the node-positive patients survived 5 years. This compares with a 5-year survival rate of 22 per cent in the node-negative patients. Although it appears that microscopic lymph node metastases impart a very poor long-term prognosis, despite lymph node dissection, Beckhurts *et al.* suggest that the median survival for the node-positive patients may still be improved by liver resection and lymph node dissection. In another prospective study, Elias *et al.*¹³ describe 100 consecutive patients undergoing liver resection and lymph node dissection for colorectal cancer metastases. None had macroscopic lymph node disease but 14 were found to have microscopic disease. This paper did not give survival data and so was not included in the present analysis, but in a subsequent abstract the 3-year actuarial survival was 26 per cent in the node-positive patients³¹.

Nordlinger *et al.*³², on behalf of the Association Francaise de Chirurgie (AFC), reported 12 of 100 patients with positive hepatic nodes surviving 5 years after liver resection for colorectal metastases. Although not included in subsequent reports from the AFC in the English language literature (and therefore not within the inclusion criteria for this review), this result is considerably more favourable than those identified by this review. One explanation may be that all 100 node-positive patients in the AFC report had completed follow-up for 5 years or more whereas follow-up was incomplete for other studies in this review. The effect of incomplete follow-up is to underestimate the numerator for 5-year survival. It is therefore important for all groups who have undertaken liver resection for hepatic metastases in

Table 2 Summary of data from 15 studies of patients undergoing curative hepatic resection for colorectal liver metastases with positive hepatic lymph nodes

Reference	Year	Total no. of hepatic resections	Operative mortality rate	Type of lymph node dissection	No. with positive nodes	5-year survival of all patients	5-year survival of node-negative patients	No. of node positive 5-year survivors
Ambiru <i>et al.</i> ¹⁹	1999	168	3.5% 60-day	'Routine dissection of the hepatoduodenal ligament'	8	26%	22%	1
Bakalakos <i>et al.</i> ²⁵	1998	301	1.1%	'Resection of simultaneous extrahepatic disease'	3	29% 5-year actuarial (for unilobar, complete resection)	Not specified	0
Beckhurts <i>et al.</i> ⁹	1997	126	1.6% 30-day	'Formal dissection of the hepatoduodenal ligament with removal of groups 12 and 13'	35	14%	27%	0
Cady <i>et al.</i> ¹¹	1992	142	5%	Portal nodes identified as positive	4	Not specified	Not specified	0
D'Angelica <i>et al.</i> ¹	1997	96 5-year survivors	Not applicable	Not stated	1	Not applicable	Not applicable	1
Hughes <i>et al.</i> ²⁰	1989	862	Not specified	'All gross disease removed... through the simultaneous removal of the lymph node groups draining the liver'	25	Not specified	32%	1
Iwatsuki <i>et al.</i> ²³	1999	305	0% 30-day	Not described	9	32.3%	Not specified	0
Jamison <i>et al.</i> ²¹	1997	280	2% 30-day	Biopsy	9	27%	37%	0
Kokudo <i>et al.</i> ¹⁹²	1999	78	Not specified	'Sampling'	9	Not specified	50%	0
Nakamura <i>et al.</i> ³⁰	1999	79	Not specified	'En bloc dissection of hepatoduodenal ligament and coeliac axis' in 43 patients	7	49%	Not specified	2
Ohlsson <i>et al.</i> ²⁶	1998	111	6%	Not specified	9	25%	Not specified	0
Petersen <i>et al.</i> ⁷	1994	66	7.6%	Nodes 'identified in specimen'	3	Not specified	36% (for the 50 with negative margins)	0
Ganchez-Céspedes <i>et al.</i> ¹⁹³	1999	21	Not specified	Not specified	5 on histo-pathology; 3 additional on molecular screening	Not specified	Median survival 1056 days	0
Savage and Malt ²⁴	1992	104	Not specified	Not specified	7	18%	Not specified	0
Yasui <i>et al.</i> ¹⁰	1995	64 (excluding 2 operative deaths and 19 with extra-hepatic disease)	2.4%	Routine hepatic lymph node dissection 'in the hepatoduodenal ligament, around the posterior pancreatic region, the common hepatic and the celiac artery'	8	Not specified	Not specified	0
Total					145			5

node-positive patients to document and report long-term outcome carefully.

Although not yet firmly established, adjuvant therapy for patients undergoing liver resection for colorectal metastases may have an important role in the future in improving long-term results^{33,34}. It is possible to achieve complete excision of macroscopic disease (R₀ resection) in many patients, including node-positive patients, although their prognosis remains poor owing to recurrence from residual microscopic disease^{14,23}. Future improvements in outcome are likely to be achieved only by a multimodal approach. Effective adjuvant therapies may render many such high-risk patients potentially curable following R₀ resection.

In conclusion, the evidence from this systematic review indicates that when metastases are found in the hepatic lymph nodes, the prognosis following liver resection for colorectal metastases is poor, even when these nodes are adequately resected. Positive hepatic nodes should be regarded in the same way as other extrahepatic disease, since long-term disease-free survival following surgery is rarely achieved. However the advent of effective surgical adjuvant therapy for colorectal hepatic metastases may change this situation in the future.

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Professor Seiki Matsuno, Chief Editor of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the January to March 2000 issues of the journal for this quarter's digest. A digest of BJS for the same period written by Professor Pierre Gullou, Associate Editor, appears in the Japanese journal.

Oesophagus

One study investigated whether the pressure variables obtained from a Swan-Ganz catheter accurately reflect the circulating blood volume just after *en bloc* resection of the thoracic oesophagus with regional lymph node dissection¹. It is well known that this operation induces severe haemodynamic changes and, although the pressure readings obtained from the catheter are an accepted means of monitoring circulating blood volume, a discrepancy between catheter data and clinical state is often experienced. The pressure variables and diameter of the inferior vena cava (IVC) and left ventricle (LV), and the central venous compliance using a Swan-Ganz catheter and echocardiography, were examined in ten patients who underwent oesophagectomy for oesophageal cancer. The central venous pressure, pulmonary arterial mean pressure and pulmonary artery wedge pressure were significantly increased just after operation compared with preoperative levels, while the diameters of the IVC and LV decreased just after operation. Compliance of the IVC decreased significantly just after operation. The haemodynamic shift to the third space after oesophagectomy induces a decrement in the compliance of the IVC. As the central venous pressure does not always reflect the circulating blood volume, measurement of the diameter of the IVC using echocardiography is extremely useful for monitoring circulating blood volume just after oesophagectomy.

Colon and rectum

The CD44 variant 6 (CD44 v6) has been postulated to be involved in both carcinogenesis and tumour progression². In this study, CD44 v6 was stained immunohistochemically in 63 colorectal cancer samples to assess significance of CD44 v6 in the carcinogenesis and progression of colorectal carcinoma. None of the normal colonocytes showed expression of CD44 v6. Expression was very strong in 24, moderate in 13 and negative in 26 tumour samples. Negative or moderate expression of CD44v6 was significantly associated with a larger tumour size ($P < 0.05$) and invasion through the bowel wall ($P < 0.01$). There was no correlation between the expression of CD44 v6 and gross type, histological differentiation, lymph node involvement, liver metastasis or clinical stage of the disease. The study showed that the expression of CD44 v6 was characteristic of neoplastic changes in the colonocytes and that diminished

expression of CD44 v6 was associated with penetration of colorectal cancer through the bowel wall, but not with either lymph node or distant metastasis.

Recent progress in laparoscopic techniques has enabled operations for various intestinal disorders to be performed under laparoscopic assistance. Interleukin (IL) 6 is an important mediator of the acute-phase response and a sensitive marker of tissue damage³. A study was conducted to investigate the fluctuation of serum cytokine and hormone levels during the perioperative period after laparoscopically assisted colectomy (LAC), and the data were compared with those obtained with conventional open colectomy. The subjects comprised eight patients who underwent open operation and eight who had LAC. Blood samples were obtained by peripheral vein puncture before the induction of anaesthesia, then at 2, 4, 6, 8, 24, 48 and 72 h after skin incision to measure the levels of serum IL-6, adrenocorticotrophic hormone (ACTH), cortisol and antidiuretic hormone (ADH). The serum level of IL-6 increased significantly during the perioperative course in both groups; however, the level 4 h after the commencement of surgery and the peak level were significantly lower in the LAC group than in the open colectomy group ($P < 0.05$). Plasma ACTH, cortisol and ADH concentrations increased rapidly in both groups, and there was no significant difference between them. The IL-6 levels in collected ascites samples were not significantly different between the two groups. Changes in serum IL-6 concentration indicate that LAC is less invasive than conventional open colectomy. These findings corresponded well with the clinical course of the patients undergoing the two types of operation.

Another study was conducted to assess the benefits of performing laparoscopically assisted surgery in 24 patients with Crohn's disease⁴, most of whom underwent ileocolic resection for ileitis and/or colitis with stenosis. Postoperative inflammatory variables for these patients were examined and compared with those of 17 patients who underwent conventional open operation. Despite giving all patients total parenteral nutrition for more than 2 weeks before operation, two patients with large inflammatory masses involving enteroenteric fistulas required conversion to laparotomy. No laparoscopic procedure was converted for adhesions after previous resection or intraoperative complications. Maximal C-reactive protein values and body temperature were significantly lower, and the time taken to normalize body temperature and leucocyte count was

significantly shorter in the laparoscopically assisted group than in the laparotomy group. The former technique should be used for patients with Crohn's disease in the inactive phase after appropriate nutritional support. The authors concluded that patients with terminal ileitis without a fistula have the strongest indication for this procedure.

The incidence and outcome of pelvic sepsis was analysed in 210 patients who underwent restorative proctocolectomy for ulcerative colitis (197 patients) and familial adenomatous polyposis (13)⁵. Pelvic sepsis developed in 18 patients (8.6 per cent) and a significantly higher incidence was seen in men than in women (13.6 *versus* 3.7 per cent respectively; $P < 0.05$). The incidence of pelvic sepsis in patients with colitis complicated by toxic megacolon and/or fulminant colitis was significantly higher than that in those with no preoperative complications (36.4 *versus* 7.4 per cent; $P < 0.05$). The incidence of pelvic sepsis following hand-sewn anastomosis was significantly higher than that following stapled anastomosis (15.6 *versus* 5.5 per cent; $P < 0.05$). The outcome of pelvic sepsis in patients with a stapled anastomosis was better than that in those with a hand-sewn anastomosis. The prognosis of women who developed pelvic sepsis was better than that of men with the complication. The risk factors predisposing to pelvic sepsis were ulcerative colitis, especially when complicated by toxic megacolon and/or fulminant colitis, and male sex, while a hand-sewn anastomosis was more vulnerable than a stapled one.

Vascular surgery

The postoperative renal function of patients who required suprarenal aortic cross-clamping during abdominal aortic surgery has been described⁶. Seven patients required unilateral suprarenal aortic cross-clamping (group A) and six needed a bilateral suprarenal clamp (group B). Eighty-three patients who required an infrarenal aortic clamp were assigned to group C. Renal hypothermia with renal perfusion or topical cooling during suprarenal clamping was not performed. No hospital deaths were encountered. In group B, the postoperative creatinine and blood urea nitrogen (BUN) level remained significantly higher than that in group C until the seventh postoperative day. Postoperative renal dysfunction (serum creatinine level greater than 2.0 mg/dl) was 28.6 per cent in group A and 50.0 per cent in group B, while it was only 8.4 per cent in group C, although no patient required either temporary or permanent haemodialysis. The postoperative peak BUN level after 30 min of suprarenal clamp time was significantly greater than that within 30 min. In summary, postoperative renal function was impaired after extended bilateral suprarenal clamping. These findings suggest that, if

prolonged renal ischaemia is expected, renal preservation should be considered.

The purpose of another study was to investigate the histological characteristics of atheromatous carotid plaque and to analyse the relationship between angiographic findings and clinical features⁷. The authors reviewed retrospectively 55 patients having carotid endarterectomy for extracranial internal carotid artery stenosis, who were treated between January 1995 and December 1997. The histological examination included haematoxylin and eosin staining, Masson-trichrome staining, and immunostaining for antismooth muscle antibody and anti-CD68 antibody. The main compositions of the carotid plaque included synthetic type vascular smooth muscle cells and extracellular matrix. The histological findings showed ulceration in 49 cases (89 per cent), calcium deposits in 42 (76 per cent) and an inflammatory reaction in 44 (80 per cent). Neurological abnormalities were strongly associated with plaque ulceration ($P = 0.045$) and an inflammatory reaction ($P = 0.013$), whereas no correlation existed with respect to calcium deposits ($P = 0.173$). The angiographic findings showed ulceration in 46 cases (84 per cent). Plaque ulceration on angiography showed no statistically significant correlation with histological findings ($P = 0.410$) and preoperative neurological abnormalities ($P = 0.059$). None of the atherosclerotic risk factors, such as hypertension, smoking, diabetes mellitus, hyperlipidaemia and myocardial infarction, had any statistically significant correlation with the histological features of the carotid plaque. In conclusion, the main composition of carotid plaque was synthetic type vascular smooth muscle cells and extracellular matrix. Histological ulceration and inflammatory reaction of the plaque showed a statistically significant correlation with the preoperative neurological symptoms, but no correlation was noted with respect to calcium deposits. Angiographic ulceration showed no correlation with histological findings or preoperative neurological abnormalities. In addition, the histological findings had no correlation with atherosclerotic risk factors.

The purpose of another study was to clarify the current aetiology and prognosis of iatrogenic vascular injuries⁸. The study involved patients who underwent surgery for vascular injury. Clinical records were reviewed retrospectively to collect information on patient profile and type of vascular injury. The surgical techniques used were classified as simple or complex. The outcome was measured as morbidity and 30-day hospital mortality due to vascular injury. The mean age of the group with iatrogenic injury was significantly greater than that of a group with non-iatrogenic injury. The numbers of men and women with iatrogenic injuries were almost equal, whereas men predominated in the group with non-iatrogenic injuries.

During the first half of the study period, more injuries were non-iatrogenic; during the second half, more were iatrogenic. Most injuries resulting from angiographic procedures could be treated by a simple repair. Injuries due to operative procedures and non-iatrogenic trauma had to be repaired by complex techniques. The overall morbidity rate was 3.8 per cent, and the 30-day hospital mortality rate 1.9 per cent. Recently developed minimally invasive surgical techniques tend to increase the risk of vascular injury, although catheterization remains the most important cause. However, as long as such injuries are treated promptly, the prognosis is good.

Lung

Fifty-nine consecutive patients with clinical stage I–III resectable small cell lung cancer (SCLC) underwent surgery with adjuvant chemotherapy based on an *in vitro* sensitivity assay between April 1982 and March 1992⁹. In 42 (71 per cent) of the patients, stable passage of cancer cells from resected specimens was possible and the sensitivity of these cultured SCLC cells to anticancer drugs was examined. In a sensitivity assay, vincristine showed the most intense specific efficacy for SCLC, followed by cyclophosphamide and cisplatin. The 5-year survival rates for patients with pathological stage I, II and III disease were 55, 33 and 23 per cent respectively. The 5-year survival rate of patients with pathological stage III disease operated on in the first 5 years was 7 per cent (one of 14). On the other hand, six (38 per cent) of 16 patients with pathological stage III lesions operated on during the second 5-year period, who were generally treated with preoperative and postoperative adjuvant chemotherapy combined with a three-drug regimen, survived for more than 5 years. In conclusion, these results suggest that combined modality therapy including surgery is necessary. Adjuvant chemotherapy combining vincristine, cyclophosphamide and cisplatin may be useful in the treatment of stage III SCLC for the purpose of achieving long-term survival with good performance status and quality of life.

The aim of another study was to evaluate whether or not perfusatory recovery of the grafted lung occurs in the early stage of convalescence from acute rejection following transplantation of a single lung¹⁰. Eight adult mongrel dogs underwent allotransplantation of the left lung with treatment of cyclosporin 10 mg/kg and azathioprine 4 mg/kg. Doppler flow probes were placed to the ascending aorta and the left pulmonary artery. Immunosuppressant therapy was discontinued to induce rejection after postoperative day 14. When the left pulmonary artery flow rate (PAFR) decreased to less than 20 per cent, methylprednisolone 20 mg/kg was administered for 3 days along with a

resumption of cyclosporin and azathioprine. Pulmonary circulation and chest radiographs were evaluated every day during the rejection episode. An open lung biopsy was also performed in each dog to obtain specimens of the grafts and native lungs for histological examination. When left PAFR decreased to less than 20 per cent, mild acute rejection was found in all dogs. Left PAFR increased significantly on the third day after methylprednisolone treatment. Thereafter, histological examination revealed minimal acute rejection in one dog and no abnormality in seven dogs. The perfusatory recovery of the grafted lung was thought to reflect the histological change in the course of convalescence.

A study was conducted to examine the efficacy and side-effects of gelatin–resorcinol formaldehyde–glutaraldehyde (GRFG) glue when used for preventing or sealing pulmonary air leakage during lung surgery¹¹. Formaldehyde–glutaraldehyde (FG) jelly was prepared by mixing FG fluid with 2.5 per cent carboxymethylcellulose to increase its viscosity. A GRFG glue-spreading stapler was employed to prevent air leakage from the staple line when cutting emphysematous lung tissue in 26 patients, 25 of whom underwent video-assisted thoracoscopic surgery and one open thoracotomy. A glue-sealing procedure was employed to stop existing pulmonary air leakage in a further 36 patients, 28 of whom underwent thoracoscopic surgery and eight open thoracotomy. The glue-spreading stapler technique prevented air leakage in all 26 patients, while the glue-sealing procedure for pulmonary air leakage stopped leakage in 31 of the 36 patients. Two patients who underwent glue sealing for air leakage from a deeply cut lung surface suffered massive pulmonary air leakage on postoperative days 1 and 6; they required repeat surgery to suture the lung fistula. A transient fever of 38–39°C developed on day 7 in six (10 per cent) of the 62 patients, but no other complications were observed. These results demonstrate that GRFG is safe and effective in preventing or stopping pulmonary air leakage in the peripheral lung, but not for stopping air leakage from a deeply cut lung.

Cardiac surgery

Tissue factor pathway inhibitor (TFPI) is a potent inhibitor of the extrinsic pathway of the coagulation cascade that is activated by cardiopulmonary bypass during open heart surgery¹². In the present study, the authors investigated whether plasma TFPI antigen levels increased during bypass in 12 patients. Plasma levels of free and total TFPI antigens were measured using an enzyme-linked immunosorbent assay, and heparin concentrations were measured with a chromogenic substrate assay. Changes in total plasma TFPI antigen concentration were significantly dependent

on the level of free TFPI antigen ($r=0.96$, $P<0.0001$), which increased significantly after heparin injection ($P<0.0001$) and increased further during the bypass period ($P<0.005$). The increased free TFPI antigen level during bypass correlated with its duration ($r=0.65$, $P=0.02$). When heparin was neutralized by protamine, the free TFPI antigen level decreased immediately, but remained higher than the preoperative level ($P<0.005$). These results suggest that plasma TFPI antigen levels increase during cardiopulmonary bypass.

General surgery

Nasal carriage of *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), is associated with an increased risk of postoperative staphylococcal infection¹³. This study was conducted to investigate the effect of preoperative nasal mupirocin treatment on postoperative infection in 141 consecutive patients undergoing upper gastrointestinal surgery between 1 March 1997 and 28 February 1998. Patients in the intervention group were treated with intranasal mupirocin three times a day for three consecutive days before operation. The incidence of postoperative staphylococcal infection in the intervention group was then compared with that in a historical control group. The control group consisted of 128 consecutive patients who underwent gastrointestinal surgery without mupirocin treatment between 1 January 1996 and 31 December 1996. The postoperative staphylococcal infection rate in the control group (11.7 per cent) was significantly higher ($P<0.001$) than that in the intervention group (0.7 per cent). The postoperative MRSA infection rate was significantly reduced by the intervention (control group 7.0 per cent *versus* intervention group 0 per cent; $P<0.01$). These results suggest that preoperative nasal eradication of *S. aureus* with mupirocin is an effective measure to prevent postoperative staphylococcal infection in patients undergoing upper gastrointestinal surgery.

The outcome of emergency abdominal surgery in elderly patients remains unsatisfactory¹⁴. Factors contributing to this outcome were studied, particularly in those aged 80 years and older (61 patients aged 80 years or more (group A) and 108 aged 65–79 years (group B)) who underwent emergency abdominal surgery between 1983 and 1997. Complications were significantly higher in group A than in group B, with respiratory failure the most common postoperative complication. The mortality rate within 30 days after operation was also higher in group A (10 per cent) than in group B (3 per cent). Complications and mortality did not differ significantly between those with and without pre-existing concomitant disease in group A. Systemic inflammatory response syndrome (SIRS) was noted in 35 patients

in group A and in 50 in group B. Severe complications occurred in 63 per cent of group A with preoperative SIRS. The mortality rate in those with SIRS was significantly higher than that in patients without. SIRS is thus a predictor of poor outcome in patients aged 80 years and older who have emergency abdominal surgery and in those aged 65–79 years. The authors concluded that patients with SIRS should initially receive minimal treatment whenever possible, rather than be overtreated, until their condition stabilizes.

Other authors carried out a prospective clinical trial of the preparation of the colon with a regimen of oral antibiotics starting on the day before operation¹⁵. Patients were assigned to one of two groups for either mechanical preparation alone (group 1, 45 patients) or mechanical bowel preparation with oral antibiotics (group 2, 38 patients). Group 2 received kanamycin and metronidazole three times on the day before operation. Cefmetazole was administered for three consecutive days as prophylaxis in both groups. Intraoperative mucosal swabs were taken; the rates of patients in group 2 with cultures yielding anaerobes or Gram-negative bacteria were significantly lower than those in group 1. There were no significant differences in the rates of patients with cultures yielding fungi or Gram-positive organisms. The positive culture rate of peritoneal fluid from group 1 was also higher than that from group 2 (40 *versus* 16 per cent; $P<0.05$). The surgical site infection rate was 18 per cent in group 1 and 13 per cent in group 2. Organisms isolated from the sites of postoperative infections were not identical with those from the peritoneal fluid. This relatively brief course of preparation minimized the emergence of resistant strains. However, in spite of the colonic bacterial burden and the intraoperative inoculation in patients with mechanical cleansing alone, the incidence of subsequent infections was comparable to that of patients who were administered oral antibiotics, provided the prophylactic antibiotic was administered for 3 days after operation.

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Editor-in-Chief

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Prospective randomized trial of low-pressure pneumoperitoneum for reduction of shoulder-tip pain following laparoscopy

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Background: Postoperative shoulder-tip pain occurs frequently following laparoscopic cholecystectomy. The aim of this randomized clinical trial was to evaluate the efficacy of a low-pressure carbon dioxide pneumoperitoneum during laparoscopic surgery in reducing the incidence of postoperative shoulder-tip pain.

Methods: Ninety consecutive patients undergoing laparoscopic cholecystectomy were randomized prospectively into low-pressure (group A) and normal-pressure (group B) laparoscopic cholecystectomy groups. Patients in group A ($n = 46$) underwent laparoscopic cholecystectomy with 9 mmHg carbon dioxide pneumoperitoneum during most of the operation, and those in group B ($n = 44$) had laparoscopic cholecystectomy with 13 mmHg pneumoperitoneum. Shoulder-tip pain was recorded on a visual analogue pain scale 1, 3, 6, 12, 24 and 48 h after operation.

Results: The low-pressure pneumoperitoneum did not increase the duration of surgery. There were no significant intraoperative or postoperative complications in either group. Fourteen patients (32 per cent) in group B and five (11 per cent) in group A complained of shoulder pain ($P < 0.05$). Mean shoulder-tip pain scores at 12 and 24 h and postoperative analgesia requirements were also significantly lower in the low-pressure laparoscopic cholecystectomy group ($P < 0.001$).

Conclusion: A carbon dioxide pneumoperitoneum pressure lower than that usually utilized to perform laparoscopic surgery reduces both the frequency and intensity of shoulder-tip pain following laparoscopic cholecystectomy.

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Introduction

Shoulder-tip pain frequently occurs after laparoscopic cholecystectomy, making postoperative recovery less comfortable. The aetiology of postoperative pain is extremely complex and a precise evaluation of the various causes is still difficult to achieve. Carbon dioxide insufflation is the commonest means of achieving pneumoperitoneum, and carbon dioxide gas is widely considered to be responsible for postoperative pain. In particular, shoulder-tip pain is presumed to be linked to carbon dioxide insufflation, and its intensity is often so strong that analgesics must be administered frequently. The reported incidence of this particularly uncomfortable type of pain varies from 35 to 63 per cent following gynaecological procedures^{1,2}. In addition, the reported incidence of shoulder-tip pain following laparoscopic cholecystectomy varies between 30 and 50 per

cent^{3,4}. Various efforts have been made to reduce these high frequencies. However, until now, none of the procedures has been proved to be practical and effective enough for routine clinical use.

To test the hypothesis that shoulder-tip pain is secondary to peritoneal stretching and diaphragmatic irritation caused by carbon dioxide, the influence of low-pressure pneumoperitoneum on the frequency and intensity of shoulder-tip pain was examined in patients undergoing laparoscopic cholecystectomy, in a prospective randomized study.

Patients and methods

Approval for the study was obtained from the local ethics committee and informed consent obtained from all patients. Randomization criteria included consecutive adult patients with American Society of Anesthesiologists physical status

grades 1 and 2 who were undergoing elective laparoscopic cholecystectomy for chronic calculous cholecystitis between January and July 1998. Five patients were excluded before randomization because an emergency laparoscopic cholecystectomy³ or exploration of the common bile duct² was planned. Laparoscopic cholecystectomy in this study was performed according to the European 'four-puncture' technique described by Dubois *et al.*⁵. Before induction of anaesthesia, patients were randomized prospectively by drawing cards labelled either 'A' or 'B'. Patients in group A underwent laparoscopic cholecystectomy with a short duration of high-pressure (13 mmHg) carbon dioxide pneumoperitoneum followed by a low-pressure (9 mmHg) carbon dioxide pneumoperitoneum, and those in group B had high-pressure (13 mmHg) carbon dioxide pneumoperitoneum all the time. In all cases the same balanced anaesthetic routine was used, including an induction drug (propofol), an opioid (fentanyl) and a mixture of 60–70 per cent air and 40–30 per cent oxygen. Neuromuscular block was facilitated with atracurium and reversed with an anticholinesterase agent (neostigmine). All procedures were performed by the same anaesthetist. In all cases residual carbon dioxide pneumoperitoneum was evacuated at the end of the procedure by compressing the abdomen, taking care to keep the trocar valves open. A drain was left for 24 h in the gallbladder fossa. Duration of surgery, intraoperative gas consumption and the occurrence of bile spillage during operation were recorded. All patients were prescribed postoperative analgesia with intravenous ketoprofen if required.

The degree of postoperative shoulder-tip pain was assessed by means of a visual analogue pain scale 1 h after the patients had been placed in the recovery room and at 3, 5, 12, 24 and 48 h thereafter. The timing of the visual analogue pain scale was not adjusted for patients receiving intravenous postoperative analgesics. The pain scale, with scores ranging from 0 (no pain) to 10 (unbearable pain), was constructed without numeration, allowing patients to mark a point along the scale that best represented their shoulder-tip pain at that time. Patients were aware that the scale served to analyse the presence and intensity of shoulder-tip pain alone and was not a representation of generalized postoperative discomfort. The frequency with which shoulder-tip pain was reported after laparoscopic cholecystectomy was also documented. Postoperative pain was assessed in a double-blinded manner: neither the patient, the assessor of shoulder-tip pain (R.C.) nor the postoperative caregivers were aware of the technique to which the patient had been randomized. The data after discharge, recorded contemporaneously by patient diaries, were collected during the first postoperative visit. Analgesic requirements of all the patients in the postoperative period

and length of postoperative hospital stay were also recorded.

The number of patients required for the study was calculated on the basis of an 80 per cent power to detect a significant difference in a major endpoint such as frequency of shoulder-tip pain or postoperative analgesia consumption at the 5 per cent significance level. The data were analysed by the use of unpaired two-tailed *t* tests and χ^2 analysis. Significance was defined as $P < 0.05$.

Results

Ninety-four patients were randomized, of whom four were withdrawn from the study as laparoscopy was converted to an open procedure.

Demographic data (age, weight, sex) were similar in both groups (Table 1). There were no differences in the mean duration of surgery, length of hospital stay or intraoperative bile spillage (Table 1). The mean carbon dioxide gas consumption for insufflation was 35.5 litres, and was significantly higher in group B (44.1 litres) than in group A (26.9 litres) ($P < 0.01$). All patients returned fully completed questionnaires.

The proportion of patients reporting postoperative shoulder-tip pain, present at any point in time during the first 48 h after operation, was 21 per cent (19 of 90 patients). Right-sided shoulder-tip pain occurred in 17 patients, and pain on both sides, moving from one shoulder to the other, in two patients. The frequency was significantly lower in the group that underwent laparoscopic cholecystectomy with a short period of high-pressure pneumoperitoneum followed by a lower-pressure pneumoperitoneum (group A) than in group B: five patients (11 per cent) *versus* 14 patients (32 per cent) ($P < 0.05$). Shoulder-tip pain started at 3–6 h and peaked in both groups at 12 h, with significant improvement after this time (Fig. 1). The frequency of shoulder-tip pain was significantly lower in group A at 6, 12, 24 and 48 h (Table 2). Pain scores, as recorded on a visual analogue pain scale, revealed that postoperative shoulder-tip pain was

Table 1 Patient details and operative variables

	Group A (n = 46)	Group B (n = 44)
Age (years)*	49.3 (22–83)	47.7 (27–78)
Weight (kg)*	66.6 (45–90)	64.3 (45–95)
Sex ratio (M : F)	13 : 33	11 : 33
Operating time (min)*	36.2 (20–55)	39.2 (30–60)
Postoperative hospital stay (days)*	1.3 (1–3)	1.4 (1–3)
No. with bile spillage	7	6

*Values are mean (range)

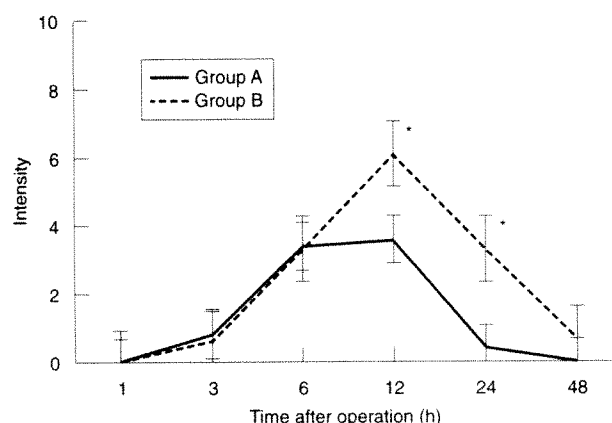


Fig. 1 Intensity of shoulder-tip pain recorded on a visual analogue pain scale for five of 46 patients who underwent laparoscopic cholecystectomy with a pneumoperitoneum of 9 mmHg and for 14 of 44 patients who underwent laparoscopic cholecystectomy with 13 mmHg pneumoperitoneum. Values are mean(s.e.m.). * $P < 0.001$ (unpaired two-tailed t test)

Table 2 Shoulder-tip pain reported in the postoperative period

Time after operation (h)	Group A (n=46)	Group B (n=44)	P
1	0 (0)	0 (0)	n.s.
3	4 (9)	4 (9)	n.s.
6	5 (11)	14 (32)	<0.05
12	5 (11)	14 (32)	<0.05
24	1 (2)	14 (32)	<0.01
48	0 (0)	7 (16)	<0.05

Values in parentheses are percentages. *Unpaired two-tailed t test; n.s., not significant

significantly less intense at 12 and 24 h in the low-pressure group (A) than in group B (Fig. 1). Mean shoulder-tip pain score approached zero in group A at 24 and 48 h compared with group B, where the mean intensity of shoulder-tip pain exceeded a score of 3 at 24 h.

In both groups there were some patients who did not require any analgesic medication (22 (48 per cent) in group A and 18 (41 per cent) in group B), with no significant differences between the two groups. Mean postoperative intravenous ketoprofen requirements were lower in group A in the 24-h postoperative period (27 versus 62.5 mg in group B, $P < 0.01$).

Apart from postoperative pain, there were no significant intraoperative or postoperative complications in either group. There was no correlation between duration of surgery and postoperative shoulder-tip pain.

Discussion

Postoperative pain at the shoulder following laparoscopic surgery is a frequent and very distressing phenomenon. The aetiology and pathogenesis of this type of pain are still not clearly understood. Some authors maintain that it may be the result of a diaphragmatic irritation of a chemical nature caused by the insufflated carbon dioxide. Carbon dioxide may be transformed, by combining with fluid in the peritoneal cavity, to an irritative carbonic acid⁶. This opinion is supported by the observation that, after laparoscopic cholecystectomy, patients experience less pain if nitrous oxide is used instead of carbon dioxide as pneumoperitoneum gas⁷. There are others, however, who believe that shoulder pain after laparoscopy could be caused by overstretching of the diaphragmatic muscle fibres owing to the high rate of insufflation. In this case, it would be the volume of the gas utilized for the pneumoperitoneum that caused the diaphragmatic irritation. A recent randomized trial demonstrated that the degree of stretching of the intra-abdominal cavity is a significant source of postoperative pain⁸, and it has been shown that a low insufflation rate significantly reduces shoulder pain⁹.

Several research studies have been carried out to find ways to reduce the frequency and the intensity of shoulder-tip pain. Many perioperative analgesic schemes have been studied¹⁰⁻¹², and the various studies have produced different results. Subcutaneous and intramuscular anaesthetic administration to the shoulder have also been studied^{13,14}; however, neither route of administration has shown sufficiently positive results to justify routine clinical use. Intraperitoneal local anaesthetics are efficient in reducing postoperative pain in laparoscopic gynaecological procedures^{15,16}, but this benefit is uncertain when applied to patients undergoing laparoscopic cholecystectomy^{3,4,17-21}. Good results in reducing this kind of pain have been obtained by intraperitoneal normal saline infusion sub-diaphragmatically at the end of the operation and, after postdeflation suction, by bupivacaine infusion in the same area³. Other studies have suggested that the heating of carbon dioxide gas to 37°C during laparoscopy reduces shoulder-tip pain²², although specific equipment is required for this purpose.

The results of this study demonstrate the effectiveness in reducing postoperative shoulder-tip pain of an extremely simple intraoperative expedient: the reduction of carbon dioxide pressure, after the introduction of the trocars, from the initial 12–13 mmHg to 9 mmHg. Whereas the incidence of shoulder-tip pain in the 13 mmHg pneumoperitoneum group was comparable with values reported in the literature, the incidence in the low-pressure group was significantly lower. The intensity of the pain recorded on a

visual analogue pain scale was also lower in patients who underwent laparoscopic cholecystectomy with low-pressure pneumoperitoneum.

These data are in agreement with those of other authors who had already found a correlation between intra-abdominal carbon dioxide pressure and postoperative pain²³. They attributed this result to the reduced gas consumption in the low-pressure group compared with that in the control group²³. Also, in the present study, the mean carbon dioxide gas consumption for insufflation was significantly lower in the low-pressure group and it is hypothesized that the reduced stretching of diaphragmatic peritoneum also helps to minimize shoulder-tip pain.

There were no significant complications in either group, and duration of surgery was comparable in the two groups. Operating at a low insufflation pressure means that the insertion of cannulas is more difficult and thus extra care is necessary to avoid injury to intra-abdominal structures. In order to reduce the operative risks, it seemed opportune to perform the initial surgical phase, the introduction of the trocars, at a higher pressure (13 mmHg), reducing pressure immediately afterwards.

Although the pain scores differed between the two groups, the number of patients who did not require any analgesic medication was similar for both groups. This lack of a direct correlation may be due to the need for analgesics for pain other than shoulder-tip pain in the early postoperative period, such as abdominal pain. There is thus a need for further research into ways to improve the quality of the postoperative care of these patients. The use of a low carbon dioxide pressure does not compromise the application of other analgesic methods to reduce the disturbance further.

In conclusion, this study demonstrates that use of the simple expedient of reducing the pressure of the pneumoperitoneum to 9 mmHg results in a significant reduction in both the intensity of postoperative shoulder-tip pain and the frequency with which it is reported. On the basis of these results, the widespread use of low-pressure pneumoperitoneum throughout most of a laparoscopic cholecystectomy procedure is recommended.

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Pilot randomized controlled study of preservation or division of ilioinguinal nerve in open mesh repair of inguinal hernia

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Background: There is uncertainty as to whether preservation or elective division of the ilioinguinal nerve influences pain and sensory loss following inguinal hernia repair.

Methods: In 20 men with primary bilateral inguinal hernias undergoing open tension-free mesh repair, the sides (right or left) were randomized for preservation or division of the ilioinguinal nerve. Patients were reviewed on day 1, 4 weeks and 6 months after operation. Any pain or numbness, as well as any loss of sensation in the area supplied by the nerve, was recorded.

Results: No significant difference was seen in pain or numbness between the divided and preserved sides. Sensory loss detected by clinical examination was more common following the division of the nerve compared with preservation.

Conclusion: Within the limitations of a small sample size, elective division of the ilioinguinal nerve during inguinal hernia repair does not appear to be associated with a significant increase in postoperative symptoms.

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Introduction

The ilioinguinal nerve is a sensory nerve that supplies the skin over the medial aspect of the thigh, upper part of the scrotum and penile root, and is normally encountered during the open repair of inguinal hernia. It is usual to preserve this nerve, but it can interfere with placement of the mesh and may be traumatized inadvertently during operation. Nerve entrapment is a cause of chronic pain following hernia surgery and division of the nerve may be required for relief¹. This investigation studied whether preservation or elective division of the ilioinguinal nerve influences pain and sensory loss after operation.

Patients and methods

In 20 consecutive men with primary bilateral inguinal hernias undergoing open repair as inpatients, the sides (right or left) were randomized to preservation or division of the ilioinguinal nerve. The randomization protocol was carried out to ensure that the more symptomatic and less symptomatic sides were included in equal numbers in each group. The study was approved by the local ethics committee and informed consent was obtained from all patients.

Both sides were repaired by a single surgeon under general anaesthesia using a tension-free mesh repair where, after reduction of the direct sac and/or excision of the indirect sac, a polypropylene mesh was placed on the transversalis fascia and secured with polypropylene sutures. The nerve was divided cleanly lateral to the deep ring where it would not interfere or come into contact with the mesh.

Patients were assessed 1 day after operation, and 4 weeks and 6 months later, for pain and any complaint of numbness at the site of repair. Pain was assessed using a visual analogue scale (0, no pain; 10, worst pain imaginable) and numbness was assessed as mild, moderate or severe. In addition light touch and pain sensation in the area of distribution of the ilioinguinal nerve were tested by an observer and any sensory loss was assessed as for numbness. The study was conducted in a double-blind fashion so that both patient and observer were unaware of the outcome of randomization.

Results

The results were analysed on an intention-to-treat basis. The mean age of patients was 65.2 (range 47–77) years. The nerve was not identified in four of 40 repairs, all on the preserved side. One patient on anticoagulant therapy developed bilateral haematomas requiring formal drainage.

Follow-up data were inadequate for four patients for the 4-week review, so these data were not included, but all patients were assessed 1 day after operation and at 6 months. The median follow-up times were 1 day, 4 (range 4–10) weeks and 6 (range 4.5–8) months.

Median pain scores using the visual analogue scale 1 day after operation were not significantly different between divided and preserved sides (2.9 (95 per cent confidence interval 1.9–3.9) and 2.5 (1.5–3.5) respectively; $P=0.98$, Mann–Whitney U test). At the 6-month follow-up, two patients complained of minor wound discomfort, one on the divided side and one on the preserved side. One patient complained of occasional episodes of sharp pain in the medial aspect of the thigh on the divided side.

Complaint of numbness over the area supplied by the nerve was not a common feature (Table 1). Only two patients complained of numbness at the 6-month follow-up, both on the divided side, but one of them had numbness over the lateral aspect of the thigh, an area not supplied by the ilioinguinal nerve. However, sensory examination revealed a degree of loss of touch and pain sensation in a number of patients not complaining of numbness, both on divided and preserved sides. However, this was more common on the divided side, especially at the 6-month visit (Table 1).

Discussion

Although preservation of the ilioinguinal nerve is desirable, it may not always be possible. Identification and elective division of the nerve away from the mesh may be preferable to its inadvertent inclusion in the sutures or to other forms of injury such as crushing, partial division or diathermy burns. The main concerns of division of a sensory nerve are chronic pain and sensory loss. However, elective division of

the ilioinguinal nerve does not appear to result in chronic groin pain. Wantz² reported that chronic groin pain was not seen following the division of the nerve in 546 hernial repairs but was seen in patients in whom the nerve had been carefully preserved. No association between long-term pain and division of the nerve was seen in another large study³, and in 100 patients with chronic groin pain following hernia repair seen at the Shouldice hospital the nerve was carefully preserved in 90 per cent⁴. Asymptomatic sensory changes are common following hernial repair³. A degree of loss of sensation in the territory supplied by the nerve was common following division in this study, occurring in 40–45 per cent of patients after 6 months compared with 5–25 per cent when the nerve was preserved. This was asymptomatic in the majority.

The present study is the first that has assessed the effect of division of the ilioinguinal nerve in a randomized setting. Patients with bilateral inguinal hernia offer an ideal population to study as the symptoms that may result from nerve division are subjective (pain, numbness) and comparison between sides by a single patient may be better than comparisons between patients. There is no evidence that elective division of the ilioinguinal nerve is associated with any significant increase in postoperative symptoms, but the limited sample size precludes any firm conclusions. One patient complained of pain on the divided side after 6 months and this might be significant if a larger number of patients were to be assessed. There is diminished sensation, especially for light touch, in the area supplied by the nerve in approximately half the patients in whom the nerve was divided, but this was not perceived by most of these patients.

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Table 1 Loss of sensation* in 20 patients undergoing bilateral inguinal hernia repair

	Day 1 (n=20)	6 months (n=20)
Numbness		
Divided side	3 (3A)	2 (2A)
Preserved side	3 (2A, 1B)	0
Loss of touch sensation		
Divided side	14 (8A, 6B)	9 (5A, 4B)
Preserved side	7 (3A, 3B, 1C)	1 (A)
Loss of pain sensation		
Divided side	11 (8A, 2B, 1C)	8 (5A, 3B)
Preserved side	6 (4A, 2B)	5 (4A, 1B)

*Severity, as perceived by the patient or determined by the blinded observer on clinical examination, is shown in parentheses: A, mild; B, moderate; C, severe

Pharmacological hepatic preconditioning: involvement of 70-kDa heat shock proteins (HSP72 and HSP73) in ischaemic tolerance after intravenous administration of doxorubicin

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Background: Pharmacological preconditioning may induce a stress response which protects liver against ischaemia-reperfusion injury (IRI). The aim of this study was to determine, in an animal model, whether intravenous administration of doxorubicin induces heat shock proteins (HSPs) in liver tissue and facilitates liver tolerance to subsequent warm IRI.

Methods: Male Wistar rats were used. Production of HSPs was determined in liver tissue sequentially after the injection of doxorubicin 1 mg/kg body-weight. Acquisition of tolerance for 30 min warm ischaemia and reperfusion of the liver was determined in animals pretreated (48 h beforehand) with doxorubicin, and in controls. Biochemical liver function and liver adenine nucleotide concentration 40 min after reperfusion and survival rate at 7 days after the ischaemic insult were recorded.

Results: Expression of HSP72 and HSP73 in the liver was confirmed 48 h after doxorubicin administration. Biochemical parameters and survival rates were significantly better in pretreated animals than in controls.

Conclusion: These results indicate that doxorubicin has the potential to provide the liver with tolerance against IRI. A simultaneous increase of both HSP72 and HSP73 in liver tissue may explain the acquisition of tolerance following the administration of doxorubicin.

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Introduction

Because of recent technical innovations in liver surgery, blood loss during parenchymal resection has become controllable, even in operations that do not use inflow occlusion of the liver¹. These innovations have decreased the number of liver operations in which inflow occlusion is absolutely necessary. However, vascular reconstruction during extensive or radical operations usually involves temporary occlusion of hepatic inflow². Lethal damage to hepatocytes occurs during and after warm ischaemia and results in postoperative liver dysfunction³. Ischaemia-reperfusion injury (IRI) therefore remains a serious problem in the field of liver surgery.

Preconditioning, such as ischaemic or heat shock preconditioning, is a new approach to the problem of IRI. The authors have previously reported that heat shock preconditioning is fairly effective in reducing subsequent IRI of the liver⁴. In Kyoto University hospital, a local method of heating the liver using a deep heating system with radio-frequency energy is now under investigation. However, this method still has some difficulties in raising liver temperature, because changes in the thermal condition of the liver are strongly attenuated by its abundant blood flow. Hence, an appropriate method to activate a stress response in the liver may be required in conjunction with clinical stress preconditioning. The stress response, which induces heat shock proteins (HSPs), is a biological response against harmful

extrinsic agents. It is conceivable, therefore, that HSPs accumulated in liver tissue are prime factors within the protective mechanism activated by stress preconditioning^{5,6}.

Among the various chemotherapeutic agents, doxorubicin, an anthracycline antibiotic, is widely used for the treatment of liver neoplasms^{7,8}. Doxorubicin exhibits its anticancer effect by blocking DNA replication and transcription through intercalation of the DNA strands⁹. At the same time, this drug is metabolized to generate reactive oxygen species^{10,11}. Therefore, it is likely that doxorubicin promotes oxidative stress, thereby inducing a stress response in cells. Previous studies have revealed that cultured cardiomyocytes or HeLa cells exhibit overexpression of HSP72 when they are exposed to doxorubicin^{12,13}. These data led the present authors to speculate whether pharmacological preconditioning with doxorubicin might activate a stress response in liver cells, and whether this drug would provide the liver with tolerance against lethal IRI.

This study investigated whether the intravenous injection of doxorubicin could trigger a stress response in rat liver and induce HSP synthesis in liver tissue, and whether preconditioning with doxorubicin would be effective in providing rat liver with ischaemic tolerance.

Materials and methods

Male Wistar rats weighing between 200 and 300 g were used in accordance with the Animal Protection Guidelines of Kyoto University.

Production of heat shock proteins

To evaluate the time course of HSP accumulation in liver tissue after doxorubicin administration, rats were killed 3, 6, 12, 24, 48, 72, 96, 120, 168 and 240 h ($n=2$ for each timepoint) after intravenous injection of doxorubicin 1 mg/kg body-weight, and liver tissue samples were collected (group 1). To control for HSP concentration in the liver tissue, liver tissue samples were collected from rats 48 h after treatment of whole-body heat shock preconditioning (42°C for 15 min) (group 2)⁴ and from untreated controls (group 3). To determine the production of HSPs in liver tissue, Western blotting analysis was employed according to the method described previously¹⁴; the examination was triplicated. The protein blots were transferred on to polyvinylidene difluoride (PVDF) membranes and incubated with monoclonal antibodies as follows: anti-HSP72 antibody (SPA-810; StressGen Biotechnologies, Victoria, British Columbia, Canada), anti-HSP60 antibody (SPA-807; StressGen Biotechnologies) and anti-HSP90 antibody

(SPA-830; StressGen Biotechnologies). The membranes were then incubated with the horseradish peroxidase-linked second antibody, antimouse immunoglobulin (NA 931; Amersham International, High Wycombe, UK). To detect protein blots of HSP73, membranes were incubated first with a monoclonal anti-HSP73 antibody (SPA-815; StressGen Biotechnologies) and then with antirat horseradish peroxidase-linked immunoglobulin (NA 932; Amersham International). Positive controls were HSP60 (SPP-740), HSP72 (SPP-755), HSP73 (SPP-750) and HSP90 (SPP-770) (StressGen Biotechnologies). The filters reacted with enhanced chemiluminescence detection reagent (ECL; Amersham International) and were exposed to X-ray film (Hyperfilm ECL; Amersham International). The spots representing each HSP on the X-ray films were scanned and quantified with an imaging densitometer (Model GS-700; BIO-RAD Laboratories, Hercules, California, USA) and analysed with PC software (Multi-Analyst/PC, version 1.1; BIO-RAD Laboratories). The data were expressed as units of optical density $\times$ square millimetres (integrated intensity).

For immunohistochemical staining liver specimens were fixed in Bouin solution overnight, immersed in ethanol to dehydrate and remove picric acid, and embedded in paraffin. Immunohistochemical staining was then performed using a primary antibody specific for the inducible-type HSP72 (SPA-810; StressGen Biotechnologies) and biotinized antimouse immunoglobulin second antibody (E-0464; Dako, Tokyo, Japan). To detect immunoreactive HSP73 in the liver tissue samples, monoclonal anti-HSP73 first antibody (SPA-815; StressGen Biotechnologies) and biotinized antirat immunoglobulin second antibody (E-0468; Dako) were used. Samples were then incubated with avidin-biotin reagents (VECTASTAIN ABC-AP Kit (Standard), AK-5000; Vector Laboratories, Burlingame, California, USA). After reacting with the substrate (VECTOR Black-Alkaline Phosphatase Substrate Kit II, SK-5200; Vector Laboratories), the slides were examined by light microscopy¹⁵.

Ischaemic tolerance

In group 1, rats were anaesthetized with an intraperitoneal injection of sodium pentobarbital 50 mg/kg body-weight and doxorubicin 1 mg/kg body-weight was then injected via the penile vein ($n=11$). The control group (group 3) received only the intraperitoneal injection of sodium pentobarbital ($n=11$). After recovery for 48 h, all animals were premedicated with an intramuscular injection of atropine sulphate (0.05 mg) and anaesthetized again with an intraperitoneal injection of sodium pentobarbital 50 mg/

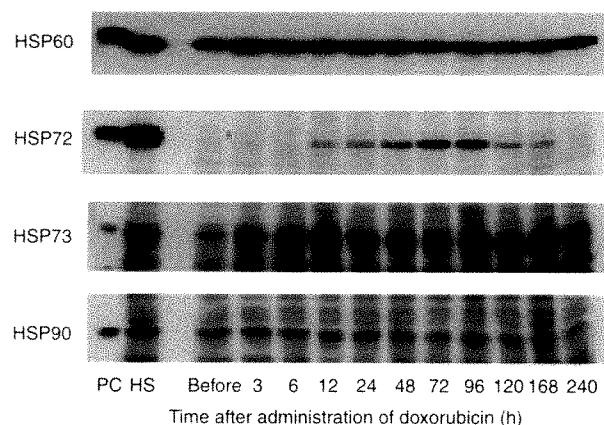


Fig. 1 Time course of the accumulation of heat shock proteins HSP60, HSP72, HSP73 and HSP90 in rat liver tissue following intravenous administration of doxorubicin. Protein concentrations are 10 µg per lane. HS, liver samples taken 48 h after heat shock preconditioning; 6 µg per lane (HSP72) and 10 µg per lane (other HSPs). PC, positive controls for HSP60 (0.05 µg per lane), HSP72 (0.01 µg per lane), HSP73 (0.2 µg per lane) and HSP90 (0.05 µg per lane)

kg body-weight. The abdomen was then opened by median laparotomy and the liver subjected to 30 min warm ischaemia by clamping the portal triad with a microvascular clamp (Pringle manoeuvre). During liver ischaemia the abdomen was temporarily closed. After 30 min the portal triad was unclamped. Blood and tissue sampling for the measurement of adenine nucleotides was performed 40 min after reperfusion ($n = 8$ for each group). For histological examination liver tissue was sampled 6 h after reperfusion ($n = 3$ for each group). After sampling, all rats were killed. The survival rate was determined in other rats ($n = 22$ in group 1; $n = 16$ in group 3). These rats were treated similarly to the rats above until unclamping of the portal triad, but were returned to their cage after abdominal closure.

Parameters and assays

Blood samples were taken from the aorta and liver samples were taken by freeze-clamping. Serum levels of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and lactate dehydrogenase (LDH) were determined in a biochemistry laboratory. Levels of adenosine 5'-triphosphate (ATP), adenosine 5'-diphosphate (ADP) and adenosine 5'-monophosphate (AMP) in liver tissue were assayed enzymatically^{16,17}. The energy charge potential (EC) was calculated according to the formula proposed by Atkinson¹⁸: $EC = (ATP + 0.5ADP)/(ATP + ADP + AMP)$. For histological examination, liver tissue samples obtained were fixed in Bouin solution, embedded in paraffin and

stained with haematoxylin and eosin. Histological changes were judged blindly by two pathologists. The survival rate of rats in each group was determined on the seventh day after hepatic warm ischaemia and reperfusion.

Statistical analysis

Student's *t* test was used for statistical analysis to determine metabolic parameters, and the χ^2 test to analyse survival rates. Values are expressed as mean(s.d.). $P < 0.05$ was considered statistically significant.

Results

Production of heat shock proteins

Liver tissue samples were placed in a polyacrylamide gel sequentially by sampling time after the administration of doxorubicin, and the time course for the expression of the four types of HSP was evaluated by Western blotting analysis. *Fig. 1* shows a representative picture of Western blotting and *Fig. 2* depicts its densitometric quantification. HSP72 was not detected in normal liver tissue, but the other three proteins of the HSP family (HSP60, HSP73 and HSP90) were expressed constitutively at low levels even in untreated rat liver tissue. After an injection of doxorubicin, HSP72 was produced between 12 and 168 h. Maximal production of HSP72 occurred between 72 and 96 h after treatment, although the levels were much lower than those after heat shock preconditioning. In contrast to HSP72, production of HSP73 increased markedly from 3 h after the administration of doxorubicin. The amount of HSP73 in liver tissue was more than double the amount in normal liver tissue. This level was maintained until 240 h after treatment. There were no significant changes in levels of HSP60 or HSP90 following treatment.

Immunohistochemical staining of rat livers using anti-HSP72 monoclonal antibody showed expression of HSP72 in both the nucleus and cytoplasm of hepatocytes after the administration of doxorubicin (*Fig. 3*). Doxorubicin induced HSP72 expression diffusely and intensely in the hepatic lobules, whereas the intense expression of HSP72 after heat shock preconditioning was limited to pericentral areas. Immunoreactive HSP73 was also detected diffusely and intensely in the nucleus and cytoplasm of hepatocytes after doxorubicin injection (*Fig. 4*). Almost all the nuclei in the hepatic lobules stained strongly for HSP73. In addition, staining of HSP73 was more diffuse in the hepatic lobules than that of HSP72. On the other hand, HSP73-positive nuclei were located mainly in the pericentral area after heat shock preconditioning. Nuclei in the periportal and mid-zonal area were negative for HSP73 staining. These

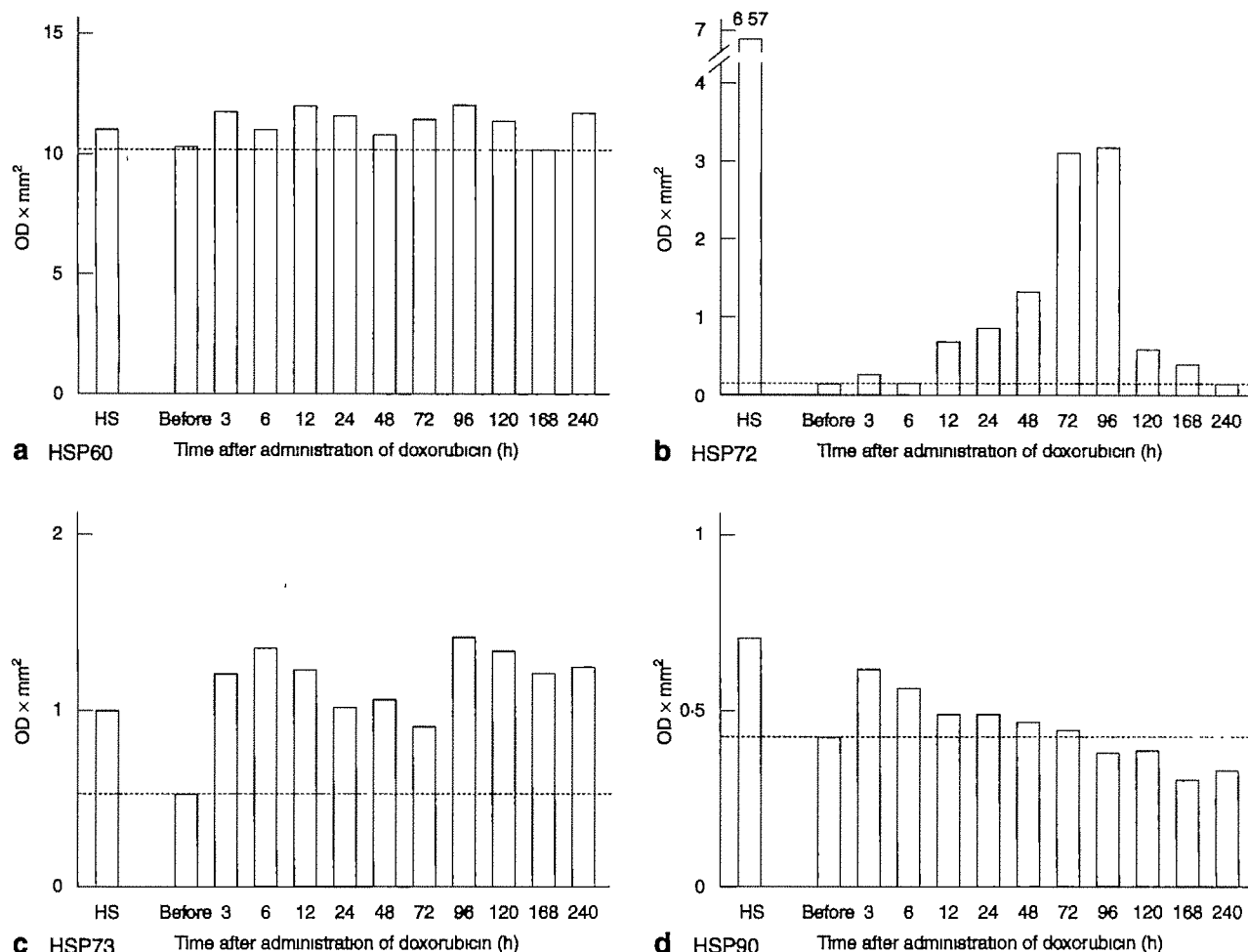


Fig. 2 Quantitative changes in heat shock proteins (HSPs) in rat liver tissue after intravenous administration of doxorubicin: **a** HSP60, **b** HSP72, **c** HSP73, **d** HSP90. Values are expressed as units of optical density (OD) × square millimetres (integrated intensity). Dotted lines indicate the levels of HSPs in the liver tissue of untreated rats. HS, liver samples taken 48 h after heat shock preconditioning

immunohistochemical observations were consistent with the results of Western blotting analysis, which showed that constitutive-type HSP73 as well as inducible-type HSP72 increased after the administration of doxorubicin.

Ischaemic tolerance

On day 7 after reperfusion the survival rate of animals was determined. After warm ischaemia the survival rate of rats in group 1 (20 of 22 animals) was significantly higher than that in group 3 (eight of 16) ($\chi^2 = 8.0$, residual d.f. 1, $P = 0.005$). Corresponding with survival rate, morphological changes after reperfusion were different in each group (Fig. 5). In control group livers, intralobular congestion and a moderate grade of central to mid-zonal necrosis were noted. In

contrast, histological changes were minimal in group 1 animals.

Table 1 shows serum levels of ASAT, ALAT and LDH. At 40 min reperfusion, all values of the examined biochemical parameters were significantly lower in group 1 than in controls (group 3). As shown in Table 2, ATP concentration and EC in liver tissue were significantly higher in group 1 animals than in controls.

Discussion

This study demonstrates changes in the stress protein metabolism of rat liver tissue before and after the intravenous injection of doxorubicin. Although many types of heat-inducible proteins appear to be involved in the stress

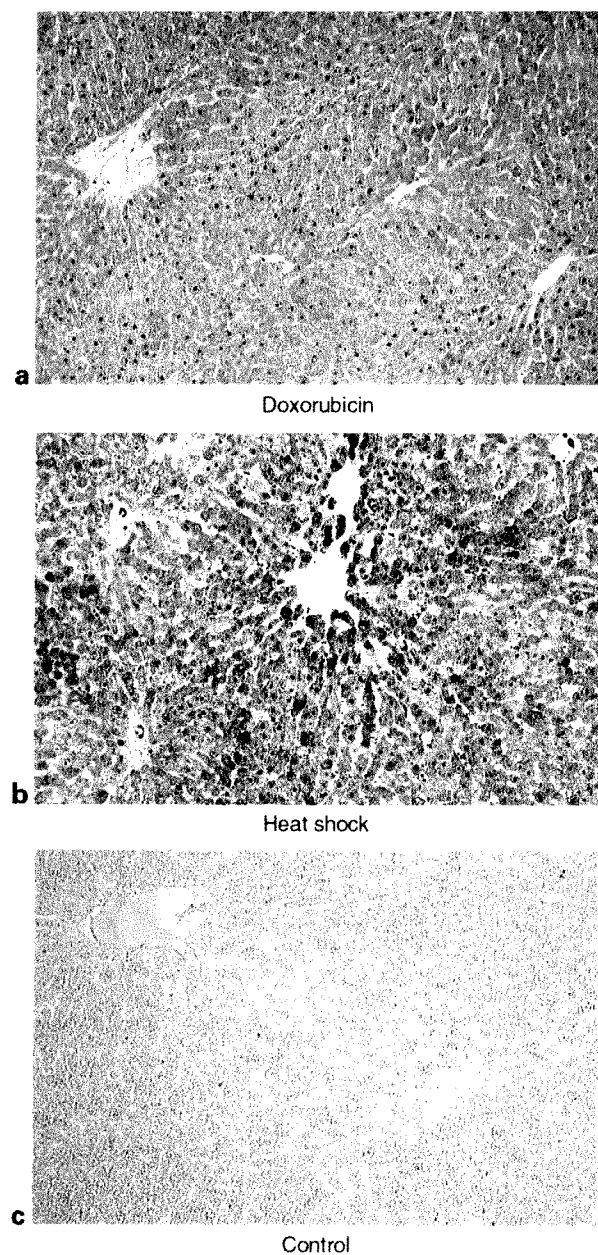


Fig. 3 Immunoreactive heat shock protein HSP72. **a** Rat liver tissue 48 h after intravenous administration of doxorubicin. Positive staining was observed diffusely in the hepatic lobules, and in both the nucleus and cytoplasm of hepatocytes. **b** Rat liver tissue 48 h after whole-body heat shock. Positive staining was observed in the nucleus and cytoplasm, and was intense in the pericentral area. **c** Control rat liver; staining was minimal. (Original magnification $\times 10$)

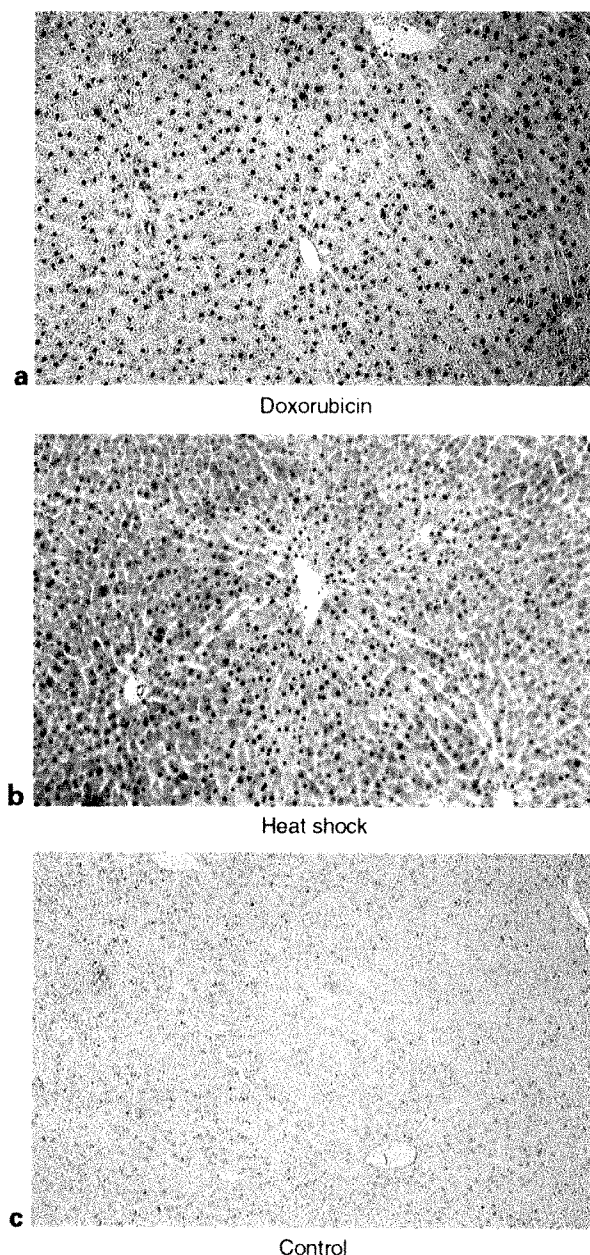


Fig. 4 Immunoreactive heat shock protein HSP73. **a** Rat liver tissue 48 h after intravenous administration of doxorubicin. Positive staining was observed diffusely in the hepatic lobules, in both the nucleus and cytoplasm of hepatocytes. **b** Rat liver tissue 48 h after whole-body heat shock; HSP73 was stained in both the nucleus and cytoplasm. In contrast to HSP72, the distribution of positive cells was diffuse. **c** Control rat livers; staining was faint. (Original magnification $\times 10$)

response of cells, this study illustrates that 70-kDa heat shock proteins, HSP72 and HSP73, are induced in rat liver tissue after the *in vivo* administration of doxorubicin 1 mg/kg body-weight. The induction patterns of HSP72 and

HSP73 after doxorubicin administration were different from the patterns observed after heat shock preconditioning¹⁴. The present study does not describe the precise mechanism responsible for HSP induction after each type

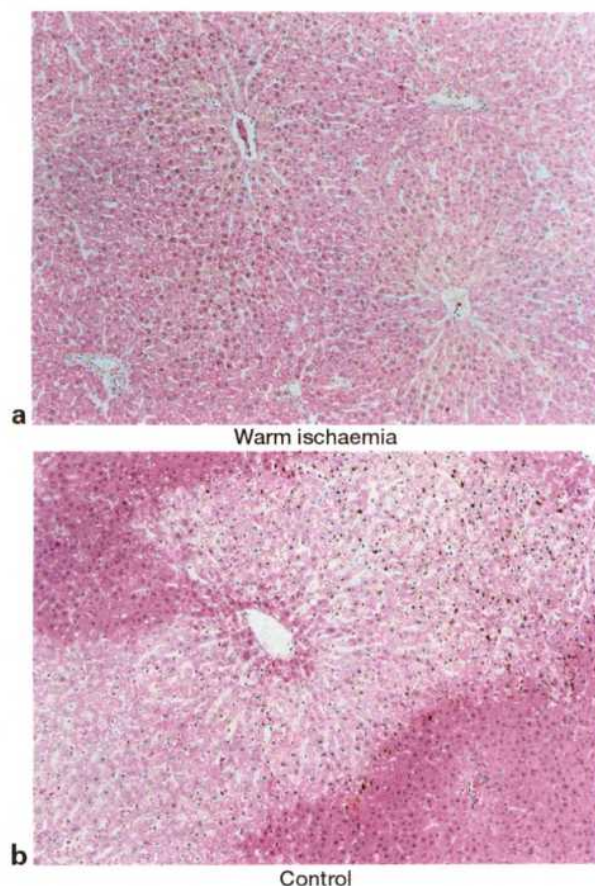


Fig. 5 Histological findings in rat liver tissue after 6 h reperfusion following 30 min warm ischaemia. **a** Congestion and necrosis were remarkably suppressed in group 1 animals, whereas **b** severe congestion and a moderate grade of central to mid-zonal necrosis were observed in controls (group 3). (Haematoxylin and eosin staining; original magnification $\times 10$)

of stress; however, there are two hypotheses that may explain the mechanisms behind these different responses. One is that each HSP has its own threshold for induction by stress¹⁹. According to this hypothesis, differences in HSP induction after heat shock or doxorubicin preconditioning are a matter of the degree of stress. Another hypothesis is that there is a qualitative difference between the mechanisms that induce stress responses from heat shock stress and from exposing chemical stress produced by doxorubicin²⁰. In developing a new method for stress preconditioning using a completely different stress from that of heat shock, it is important to pay special attention to these qualitative and quantitative factors within cellular responses.

It has been generally acknowledged that *de novo* synthesis of HSP is triggered by the activation of a heat shock factor^{21–23}. In the initial phase of the transcriptional response, the 'stress sensor' of the cell may be involved.

Table 1 Serum levels of aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase after 40 min reperfusion

	Doxorubicin pretreated	Controls	P*
ASAT (units/l)	1 908(437)	2 527(478)	0.017
ALAT (units/l)	1 985(486)	2 797(768)	0.024
LDH (units/l)	17 295(3534)	25 025(7866)	0.024

Values are mean(s.d.). ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; LDH, lactate dehydrogenase ($n = 8$). Normal values of these parameters in rat serum ($n = 6$): ASAT 67(13) units/l, ALAT 54(7) units/l, LDH 226(57) units/l. *Student's *t* test

Table 2 Concentration of adenosine 5'-triphosphate and energy charge potential in liver tissue after 40 min reperfusion

	Doxorubicin pretreated	Controls	P*
ATP ($\mu\text{mol/g}$ wet tissue weight)	2.27(0.51)	1.38(0.30)	0.0008
Energy charge potential	0.77(0.03)	0.67(0.06)	0.0007

Values are mean(s.d.). ATP, adenosine 5'-triphosphate ($n = 8$). Normal values of these parameters in rat liver tissue ($n = 6$): ATP 3.52(0.13) $\mu\text{mol/g}$ wet tissue weight, energy charge potential 0.83(0.01). *Student's *t* test

However, the actual mechanism by which cells recognize thermal or other stress is not clear⁵. The endpoint of pharmacological preconditioning is to facilitate a molecular reaction within the stress response by an adequate stimulation of the 'stress sensor' in the target cells. The cytotoxicity of doxorubicin is reportedly related to the formation of a semiquinone free radical^{24–26}. After intravenous administration, doxorubicin accumulates in the liver and is metabolized²⁷. The metabolites are then excreted into bile and enter the enterohepatic circulation²⁸. Therefore, it is possible that a large amount of doxorubicin primarily attacks hepatocytes and promotes oxidative stress, thus inducing HSP72 and HSP73. This property of doxorubicin may be advantageous in the intensive stimulation of hepatic responses, and may result in the overexpression of HSP72 and HSP73 for more than 96 h after administration.

The present results suggest that preconditioning of the liver by doxorubicin administration could improve liver function after a 30-min *in situ* occlusion of the total hepatic circulation. Hepatocytes maintained a high-energy status during reperfusion, and cellular damage was avoided. Hence, doxorubicin preconditioning appears to improve the survival rate of rats following lethal IRI of the liver. This outcome was quite similar to that of heat shock⁶ or ischaemic¹⁴ preconditioning, although the types of stress

in these preconditioning methods were completely different. It has already been reported that after experiencing thermal stress cells acquire cross-tolerance to various kinds of injury²⁹. Based on evidence suggesting that a previously induced HSP plays an important function in this cross-tolerance³⁰, a prime factor for tolerance acquisition after heat shock and doxorubicin preconditioning can be explained simultaneously by the effects of induced HSPs. In this study, it is reasonable to explain the protective effect of doxorubicin preconditioning by the induction of HSP72 and HSP73, because both were induced from chemical effect of doxorubicin. Although little has been clarified about the exact function of HSP73, studies have proved that HSP72 and HSP73 are closely related in their physiological roles and perform similar functions³¹. HSP73 is expressed constitutively in cytoplasm under non-stress conditions. So, it is likely that HSP73 has a special function in regulating activation of heat shock factors which trigger the transcriptional response of HSP. During the course of 70-kDa HSP induction, it has been reported that endogenous levels of HSP73 and HSP72 may modulate the integrity of HSP induction³². That is, the levels of HSP72 and HSP73 interdependently affect the signals for induction of each other. Kawagoe *et al.*³³ reported that the balance of HSP72 and HSP73 messenger RNA induction is an important factor for the tolerance or vulnerability of the cells during transient ischaemia. Aquino *et al.*³¹ reported that HSP72 partially compensates for the decreased chaperoning function of HSP73. Taken together, induced HSP72 and HSP73 function cooperatively to provide ischaemic tolerance of the liver after pharmacological preconditioning by doxorubicin.

The chaperoning function of 70-kDa HSPs is vital in protecting the functions of intracellular proteins, although the precise mechanism is complicated and not yet completely understood. A previous study¹⁵ showed that protein denaturation from the attack of reactive oxygen species, which was coupled with lipid peroxidation, was significantly attenuated by heat shock preconditioning. This suggests that the existence of HSP72 or HSP73 protects the cells at the level of cytoplasmic proteins.

In the clinical application of pharmacological preconditioning with doxorubicin, ideal preconditioning was attained with the dose administered. That is, the beneficial function of a stress response was initiated before the deleterious side-effects of the chemical occurred. At 48 h after doxorubicin administration (1 mg/kg body-weight), toxic side-effects in the liver were not apparent. The beneficial effect of preconditioning against lethal IRI prevailed.

Considering the possibility of clinical application of pharmacological preconditioning with doxorubicin, a

doxorubicin dosage of 1 mg/kg body-weight was used, which is the same as that currently employed for clinical chemotherapy against hepatocellular carcinoma, without significant adverse effects. This study showed that the dose in current clinical use without adverse effects is efficacious in producing the beneficial effect of preconditioning against lethal IRI. Of course, preconditioning with drugs has particular disadvantages. Physical stimulation such as heat shock preconditioning can be applied to a local anatomical area, and its duration can easily be regulated by external apparatus. However, with chemical stimulation the stress response is highly dependent on the metabolic kinetics of the drug. Therefore, determination of appropriate individual dosage requires special care, especially in the case of metabolic liver dysfunction. In spite of these problems, doxorubicin has the potential to produce excellent results in patients with liver cancer.

In conclusion, doxorubicin has the potential to provide the liver with tolerance against IRI. Within the mechanism of this beneficial action of doxorubicin, the cooperative production of HSP72 and HSP73 appears to be involved. Although HSP72 is the main molecular chaperone induced after heat shock preconditioning, HSP73 is implicated in the protective mechanism of the liver against IRI after pharmacological preconditioning with doxorubicin in conjunction with HSP72.

Acknowledgements

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Prospective analysis of a scoring system to predict choledocholithiasis

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Background: The management of choledocholithiasis in the laparoscopic era remains debatable. A common policy is to perform preoperative endoscopic retrograde cholangiopancreatography (ERCP) on patients suspected of having common bile duct (CBD) stones, using standard risk criteria. The aim of this study was to evaluate prospectively a scoring system designed to improve the accuracy of CBD stone prediction before laparoscopic cholecystectomy.

Methods: Known clinical, biochemical and radiological risk factors for CBD stones were analysed retrospectively in 233 patients. The presence ($n=77$) or absence ($n=156$) of CBD stones was determined by preoperative ERCP and/or laparoscopic cholangiography. Using multivariate analysis, the significant risk factors for CBD stones were identified and a new preoperative scoring system was developed. A score of 3 or more was taken as the cut-off point to suggest CBD stones and the need for preoperative ERCP. This scoring system was then tested prospectively in 211 consecutive patients with symptomatic gallstones requiring surgery. Patients whose bile ducts could not be demonstrated by ERCP or operative cholangiography were excluded.

Results: Fifty-five patients scored 3 or more (predicted ERCP rate of 29 per cent), of whom 23 (42 per cent) had proven CBD stones. Intraoperative cholangiography was successful in 87 per cent. Five patients (4 per cent) who scored less than 3 had small stones (less than 5 mm) demonstrated at operative cholangiography. The overall sensitivity and specificity of this scoring were 82 and 80 per cent respectively.

Conclusion: Formal risk assessment of the presence of CBD stones using this scoring system is simple and may be used for preoperative selection of patients for biliary tract imaging by magnetic resonance cholangiography or ERCP.

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Introduction

Laparoscopic cholecystectomy is now the conventional method for treatment of patients with symptomatic gallstones^{1–4}. The optimum management of choledocholithiasis in these patients is, however, debatable. The reported incidence of common bile duct (CBD) stones varies between 7 and 20 per cent^{1,5–7}, but there has been a fall in the reported incidence of CBD stones with the introduction of laparoscopic surgery^{8,9}. Whether this is a real reduction as a result of the earlier diagnosis and treatment of patients with gallstones¹⁰, or an apparent one due to difficulty in diagnosis of CBD stones, has yet to be established.

A widely adopted policy is to subject patients considered to be at high risk of CBD stones to preoperative endoscopic retrograde cholangiopancreatography (ERCP). The criteria for ERCP were established during the open cholecystectomy era and were based on recognized clinical, biochemical and ultrasonographic abnormalities^{5,6}. Using these criteria, bile duct stones may be positively identified at ERCP in only 10–60 per cent of cases^{7,11}. Consequently a large number of patients undergo unnecessary ERCP with an attendant potential for morbidity and occasional death.

Several studies have been performed, aimed at improving the accuracy of diagnosis of CBD stones, with variable results^{5,11,12}. Often there is inconclusive evidence as to the absence of CBD stones because of low rates of intraopera-

tive cholangiography. Stones are assumed to be absent if the patient remains asymptomatic in the short term, but such patients may present with significant complications at a later date. In the initial part of this study, risk factors were selected that incorporated standard criteria (i.e. clinical presentation, liver function tests and abdominal ultrasonographic findings) and were used retrospectively to develop a scoring system. The purpose of this scoring system was to increase the accuracy of CBD stone detection and thereby to rationalize the number of patients undergoing preoperative ERCP. A prospective evaluation of this scoring system is the subject of the second part of this study.

Patients and methods

Laparoscopic cholecystectomy with intraoperative cholangiography using a standardized method¹³ is routinely carried out by two surgeons at Dumfries and Galloway Royal Infirmary. A retrospective analysis was carried out of 233 consecutive patients with definite documentation of the presence ($n=77$) or absence ($n=156$) of CBD stones at ERCP or laparoscopic cholangiography between October 1992 and December 1994. Age, sex, clinical presentation, liver function tests (bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels) and ultrasonographic findings were recorded. All patients had liver function tests performed within 6 weeks of the ERCP or laparoscopic cholecystectomy. The factors analysed in the univariate and multivariate analysis are shown in *Table 1*. The factors found to be significant in the multivariate analysis were incorporated into a scoring system, with the score for each factor based on the coefficients in the logistic regression analysis. Thus a simple scoring system was established that could be readily adopted in the clinical setting (*Table 2*). A cut-off point of 3 or more on this scoring system yielded the least number of false negatives (i.e. the greatest sensitivity) without markedly increasing the number of false positives, correctly predicting 145 of the 156 patients in the retrospective group without CBD stones. Thus, if a patient scores less than 3, there is a low risk of CBD stones and preoperative ERCP is deemed unnecessary.

A prospective evaluation of this scoring system was carried out between April 1996 and December 1997 in 211 consecutive patients undergoing laparoscopic cholecystectomy. The purpose of this prospective study was to test the scoring system prospectively in an entirely different group of patients and to evaluate the cut-off point used to select patients for ERCP. The protocol used in the management of these patients is shown in *Fig. 1*, but early treatment was employed in selected inpatients during the same admission (e.g. severe acute pancreatitis). ERCP was carried out

within 6 weeks and elective cholecystectomy within 3 months.

Statistical analysis

The univariate association between presence of CBD stones and other factors was tested using the χ^2 test with Yates' correction for binary factors and the Mann-Whitney *U* test for ordinal or quantitative factors. Stepwise multiple logistic regression was used to identify factors that significantly predicted the presence of stones after adjusting for others, and weighting for the predictive scores was set to round numbers approximately proportional to the coefficients of the final logistic model.

Results

A total of 211 patients (59 men and 152 women) were evaluated prospectively using the clinical management protocol shown in *Fig. 1*. Indications for cholecystectomy were biliary colic (140 patients), acute cholecystitis (26), jaundice current and resolved (9 and 12 patients respectively), acute pancreatitis (21) and ascending cholangitis (three). Some 187 patients underwent successful laparoscopic cholecystectomy, with conversion to open surgery in 12 patients (conversion rate 6 per cent). A further 12 patients proceeded directly to open cholecystectomy as they had previously undergone complex or multiple abdominal operations. Intraoperative cholangiography was successful in 184 patients (87 per cent). Among the 27 cholangiography failures, seven patients had undergone ERCP before the operation, but the 20 patients who had no form of bile duct imaging were excluded from further analysis. In all, 136 patients scored between 0 and 2 and thus did not undergo preoperative ERCP. Fifty-five patients scored 3 or more and underwent successful ERCP before cholecystectomy. The 23 patients with CBD stones were successfully managed endoscopically but in two patients more than two attempts at ERCP were needed to clear the duct of stones. There were no deaths related to ERCP or laparoscopic cholecystectomy. Two patients had mild pancreatitis after ERCP, which resolved uneventfully.

The distribution of scores acquired by patients is shown in *Fig. 2*. The preoperative ERCP rate using the scoring system was 29 per cent. Of the 55 patients with a score greater than 3, 23 (42 per cent) were found to have CBD stones. Of the 136 patients with a score of 0–2, five (4 per cent) were found to have CBD stones by laparoscopic cholangiography. Of these five patients, four had a score of 0 and one had a score of 2 for age and male sex. The size of stones in these five patients was less than 5 mm. Although all these patients were asymptomatic, two underwent a post-

Table 1 Retrospective analysis of 233 patients showing the univariate and multivariate association between common bile duct stones and other factors

Factor	No. with stones (n=77)	No. with no stones (n=156)	Percentage with stones	P	
				Univariate	Multivariate
Age (years)					
<55	12	83	13	<0.001	<0.05
>55	65	73	47		
Sex					
F	51	138	27	<0.001	<0.05
M	26	18	59		
Jaundice					
Absent	50	146	26	<0.001	<0.05
Resolved	18	9	67		
Present	9	1	90		
Ascending cholangitis					
Absent	68	154	31	<0.001	<0.05
Present	9	2	82		
Pancreatitis					
Absent	70	150	32	n.s.	n.s.
Present	7	6	54		
Alkaline phosphatase level					
Normal	26	141	16	<0.001	n.s.
Greater than normal but less than double	17	14	55		
Greater than double	34	1	97		
Bilirubin level					
Normal	40	153	21	<0.001	n.s.
Greater than normal but less than double	13	1	93		
Greater than double	24	2	92		
Transaminase levels					
Normal	41	151	21	<0.001	<0.01
Greater than normal but less than double	9	3	75		
Greater than double	27	2	93		
Duct diameter on ultrasonography					
Normal	38	152	20	<0.001	<0.001
Dilated	39	4	91		
Common bile duct stone on ultrasonography					
Absent	60	155	28	<0.001	<0.05
Present	16	1	94		

n.s., Not significant

operative ERCP at which no stones were detected in the biliary tree. The other three patients have remained asymptomatic over a period of 39, 34 and 30 months to date.

The overall incidence of CBD stones in this study population was 15 per cent. Using a cut-off of 3 or more points on the scoring system, the sensitivity and specificity of detecting CBD stones before operation were 82 and 80 per cent respectively. The use of a cut-off point of 2 or more to select patients for ERCP would have decreased the number of patients with false-negative findings from five to four, at the cost of 24 additional negative ERCPs. *Table 3*

gives details of the sensitivity and specificity of this scoring system at different cut-off points, suggesting that the cut-off of 3 or more used in this study is to be preferred.

Discussion

This study highlights the difficulty of being able to identify CBD stones accurately before operation, but nevertheless shows the benefits of using established criteria incorporated into a scoring system in an attempt to avoid unnecessary preoperative ERCP. ERCP has the advantage over in-

Table 2 Predictive scores for each multivariate factor used to produce the scoring system

Factor	Criteria	Score
Age	<55 years	0
	≥55 years	1
Sex	F	0
	M	1
Jaundice	Absent	0
	Resolved	1
	Current	2
Ascending cholangitis	Absent	0
	Present	3
Transaminases	Normal	0
	Greater than normal but less than double	2
	Greater than double	4
CBD diameter (ultrasonography)	Normal	0
	Dilated	3
CBD stone (ultrasonography)	Absent	0
	Present	3

CBD, common bile duct

Outpatients

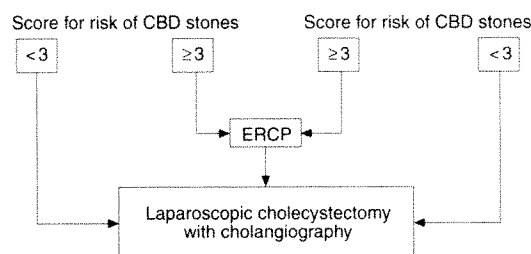
Patients with symptomatic gallstones need:

1. Recent ultrasonography
2. Current LFTs

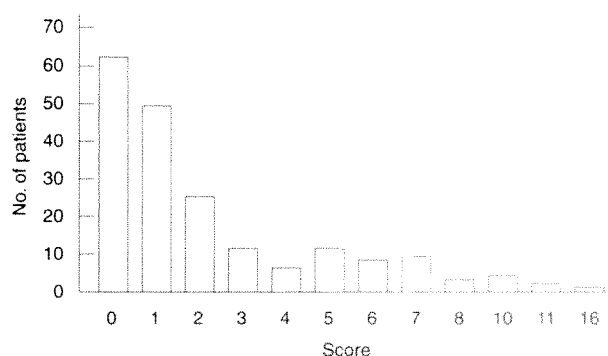
Inpatients

Patients with acute symptomatic gallstones who settle on conservative treatment

Review at 1 month
Repeat LFTs

**Fig. 1** Protocol for the prospective evaluation of patients who present with gallstones. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; LFT, liver function test

travenous cholangiography of being therapeutic¹⁴ but is associated with a complication rate of 5–10 per cent, particularly if endoscopic sphincterotomy is performed^{15,16}. Laparoscopic exploration of the CBD is an evolving technique not routinely practised, but successful laparoscopic duct clearance has been reported in over 60 per cent of cases in specialist centres^{1,17,18}. CBD stones detected at laparoscopic cholangiography may be dealt with by postoperative ERCP, but there is a potential risk of cystic stump leakage secondary to distal obstruction from

**Fig. 2** Distribution of scores acquired by patients before laparoscopic cholecystectomy**Table 3** Sensitivity and specificity of the scoring system at different cut-off points, showing an optimum cut-off point of 3 or more

Cut-off point	Sensitivity (%)	Specificity (%)
≥2	86	66
≥3	82	80
≥4	68	85
≥5	57	86

retained stones, especially if there has been an inadequate closure of the cystic duct stump¹⁹. There is also the risk of failure to clear such stones endoscopically at a later date. Other newer imaging techniques, such as magnetic resonance (MR) cholangiography, have shown promising results²⁰ in the detection of CBD stones. MR cholangiography, although non-invasive, is expensive and currently not readily available throughout the UK.

The management of asymptomatic CBD stones is debatable. In one study 55 per cent of patients with untreated CBD stones presented with biliary related complications during a maximum follow-up of 13 years²¹. Other studies have demonstrated significant complication rates from retained or silent bile duct stones on long-term follow-up^{22–24}. Other studies have suggested that asymptomatic CBD stones can be safely left alone^{25,26}, but it is generally considered that potentially serious complications of leaving stones in the duct should be avoided.

Several studies have tried to improve the accuracy of diagnosis of CBD stones by assessment of clinical, biochemical and ultrasonographic criteria, with variable results. Barkun *et al.*⁴ generated a predictive model for selecting patients for preoperative ERCP. Using logistic regression, the best model for predicting bile duct stones at ERCP included the following independent predictors: age

over 55 years, raised bilirubin concentration (over 30 $\mu\text{mol/l}$), CBD dilatation and a CBD stone seen on ultrasonography. The probability of finding ductal stones at ERCP ranged from 8 per cent when none of these predictors was present to 94 per cent when all four were present. The rate of intraoperative cholangiography, however, was only 4 per cent during the period of study, and therefore confirmation of the presence or absence of CBD stones was not possible in patients who did not undergo ERCP. Low rates of cholangiography, common to other studies, may mean that a number of CBD stones are missed and these patients may present later with complications. The strength of the present study is that all patients underwent either ERCP or operative cholangiography to establish clearly whether or not CBD stones were present.

The clinical factors found to be significant in this study were jaundice and ascending cholangitis. The finding that resolved jaundice was less significant is to be expected and is compatible with the findings of Rijna *et al.*¹¹, who found that none of 13 patients with resolved jaundice had CBD stones. This group also found ascending cholangitis to be significant and that pancreatitis was significant only in the acute phase. In the present study the majority of patients with acute pancreatitis did not undergo ERCP as determined by the severity of the attack, which may explain why pancreatitis was not found to be significant in either the univariate or the multivariate analysis. Other studies have supported these findings, on the basis that patients with gallstone pancreatitis are likely to have passed the stone spontaneously^{16,27-30}.

Previous studies have found biochemical parameters useful in predicting the presence of CBD stones, but there is considerable variation between studies^{4-6,16}. Serum bilirubin concentration has been consistently identified as a significant predictive factor^{5,16} and was also found to be so in the univariate analysis conducted in the present study. However, the significance of increased serum bilirubin levels was lost in the multivariate analysis. This may be due to the close association between serum bilirubin concentration and jaundice, leading to the exclusion of the former, as is a feature of multivariate analysis. In the present study the serum transaminase concentration and ultrasonographic abnormalities were found to be significant predictors of CBD stones. If serum transaminase levels were more than twice the normal value, patients scored higher than those with current jaundice, owing to the weighting for the predictive scores being proportional to the coefficients of the final logistic model. CBD dilatation was a significant predictive factor, in keeping with the findings of several other studies^{4-6,27}. Conversely, the sensitivity of ultrasonography in determining the presence of CBD stones was low, between 19 and 55 per cent³¹.

The incidence of CBD stones in this population was 15 per cent. Despite a selective ERCP policy dictated by the scoring system, CBD stones were present in only 42 per cent of patients. It is well established from the experience of endoscopists that stones migrate fairly rapidly out of the CBD during or soon after the acute episode²⁷⁻³⁰, and this may explain a detection rate of less than 50 per cent in this group of patients as the time interval between the scoring of patients and ERCP may have been as long as 6 weeks. Stones were detected at intraoperative cholangiography in five patients (4 per cent) who did not qualify for preoperative ERCP. Using the scoring system the sensitivity and specificity of detecting CBD stones before operation were 82 and 80 per cent.

In conclusion, several risk factors have been identified as significant predictors of the presence of CBD stones and these have been incorporated into a scoring system. This could be readily adopted into the clinical setting in an attempt to rationalize the use of preoperative ERCP or to target patients for non-invasive imaging techniques such as MR cholangiography.

Acknowledgements

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Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma

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Background: Cholangiocellular carcinoma is an uncommon primary liver cancer, which may be mixed with hepatocellular carcinoma. A retrospective analysis was undertaken to evaluate the results of surgical treatment and to identify prognostic factors.

Methods: Between 1978 and 1996, 162 patients underwent surgery for cholangiocellular carcinoma: liver resection ($n=95$), liver transplantation ($n=24$) and exploratory laparotomy with and without drainage ($n=43$). Univariate and multivariate analyses of prognostic factors were performed.

Results: Overall survival was 47 per cent at 1 year, 28 per cent at 2 years and 13 per cent at 5 years. Survival rates for patients with resectable tumours were 64, 43 and 21 per cent respectively, and for those who underwent liver transplantation 21, 8 per cent and zero respectively. Univariate analysis showed that the following variables had an effect on survival: age, jaundice, liver resection, T, N and M stage in the tumour node metastasis classification, Union International Contra la Cancrum (UICC) tumour stage, tumour-free margins, vascular infiltration, tumour number, tumour size and serum level of carcinoembryonic antigen. Multivariate analysis identified jaundice, N and M category, and UICC tumour stage as independent prognostic factors.

Conclusion: The data underscore the importance and prognostic value of the UICC tumour classification for cholangiocellular carcinoma. The prognosis of mixed tumours is no different. Liver resection remains the treatment of choice; transplantation offers no solution for otherwise unresectable tumours.

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Introduction

In an autopsy study published in 1954, Edmondson and Steiner¹ differentiated primary liver cancers into those originating from hepatocytes and those arising from bile duct epithelium. In addition, they described an uncommon 'subvariety' centrally located in the liver hilum and causing biliary obstruction. Currently, the Union International Contra la Cancrum (UICC) uses two subclassifications that separate bile duct cancer or cholangiocarcinoma into an intrahepatic and extrahepatic type². Intrahepatic bile duct carcinoma, itself an uncommon primary liver cancer, is

classified in accordance with the same rules as hepatocellular carcinoma (HCC). Although the synonyms intrahepatic bile duct carcinoma and peripheral cholangiocarcinoma are widely used^{3–8}, other authors prefer the term cholangiocellular carcinoma (CCC), which brings out the affinity to HCC^{9–13}.

CCC has no particular clinical or radiographic characteristics^{13–16}. Abdominal pain and weight loss are the predominant symptoms^{13,14}. Prognosis is very poor, with a reported median survival time of 2 months from diagnosis¹³. Yamanaka *et al.*¹⁷ have recently proposed a clinicopathological subclassification of CCC into three types¹⁷: type I, no biliary stricture; type II, biliary stricture without jaundice; and type III, biliary stricture with jaundice. In type III, differentiation from extrahepatic carcinoma of the hilar

The editors have satisfied themselves that all authors have contributed significantly to this publication.

bifurcation ('Klatskin' tumour) may be very difficult^{1,18}. Mixed tumours, containing components of both HCC and CCC, and combined coexisting HCC and CCC have also been described^{19,20}. Risk factors for the development of CCC are cystic dilatation of the biliary tract, stone formation, sclerosing cholangitis and, in Eastern countries, parasitic infection with *Opisthorchis viverrini* and *Clonorchis sinensis*. Furthermore, an association with the erstwhile contrast medium thorium dioxide (thorotrast) has also been found²¹. In the literature of the past few years there is a consensus that the treatment of choice is surgical resection, while the role of liver transplantation for unresectable tumours has been controversial^{3-11,22,23}. The present study analyses the experience of a single centre with regard to prognostic factors in treatment of CCC.

Patients and methods

Between July 1978 and December 1996, 162 patients underwent surgery for CCC of the liver. Tumour resection was performed in 95 patients. In 24 patients, with tumours considered to be unresectable, total hepatectomy and subsequent liver transplantation was performed. Forty-three patients underwent exploratory laparotomy only or with various types of surgical drainage. The inclusion criterion for exploratory laparotomy was biopsy-proven adenocarcinoma of the liver when an extrahepatic primary tumour had been excluded unequivocally by endoscopy and diagnostic imaging.

The clinicopathological data of the 162 patients who underwent surgery for CCC were evaluated. The tumour, lymph node and distant metastases (TNM) stages were evaluated in accordance with the UICC². The residual tumour classification was used to define the presence or absence of residual tumour after resection (R_1 signifies microscopic, R_2 macroscopic and R_0 no residual tumour). The Yamanaka classification was used to identify tumours associated or unassociated with biliary obstruction, with and without clinically evident jaundice¹⁷. Liver cirrhosis was classified in accordance with the Child-Pugh classification²⁴. The patient's general state of health was noted. A high-risk group was defined on the basis of diabetes, cardiovascular, pulmonary and renal disease. Adjuvant chemotherapy was occasionally given, but neither adjuvant nor multimodal treatment was standardized.

Patient, clinical and pathological demographic data as well as information on tumour characteristics, treatment modalities and outcome were obtained retrospectively by reviewing patient records. Complete information on survival was available for 159 of the 162 patients. Follow-up data were available up to January 1998, by which time 133 patients (82 per cent) had died. Twenty-six patients (16

per cent) were still alive (24 resection, one transplantation, one exploratory laparotomy). The precise time of tumour recurrence and pattern could not be determined in the majority of patients. Complete information about the cause of death was available in 81 patients (61 per cent). An autopsy was performed on nine patients. In one patient, who died in the postoperative period after extended left hemihepatectomy, exact tumour staging was not available.

Statistical analysis

Patient survival was calculated using the Kaplan-Meier method. Surgical mortality was defined as death within 30 days of operation. Because information was incomplete, tumour-free survival was not calculated. For patients who underwent resection or transplantation, the relationship between each defined clinicopathological variable and survival was calculated by use of the log rank test; $P < 0.05$ was considered significant. To identify independent prognostic factors, only those variables that were statistically significant by univariate analysis were included in the multivariate analysis. Multivariate analysis was performed using stepwise Cox proportional hazards regression. The prognostic factors were derived from the last step of the regression analysis. $P < 0.05$ was considered significant.

Results

Fourteen (9 per cent) of the 162 patients had a mixed HCC/CCC. In 23 patients (14 per cent) the tumour was accompanied by liver cirrhosis. The risk group with significant co-morbidity comprised 27 patients (17 per cent). Seventeen patients (10 per cent) presented with jaundice at the time of diagnosis. Levels of the tumour marker carcinoembryonic antigen (CEA) were raised in 17 (18 per cent) of 95 patients (median 2 (range 0-175) $\mu\text{g/l}$); α -fetoprotein (AFP) levels were raised in 24 (24 per cent) of 98 patients (median 4 (range 0-985) IU/ml) and carbohydrate antigen (CA19/9) levels were increased in 58 (70 per cent) of 83 patients (median 48 (range 0-21 310) units/ml).

Ten of 23 patients with liver cirrhosis underwent hepatic resection (Child A, eight; B, two) and nine underwent liver transplantation (Child A, one; B, eight). In the high-risk group, 20 patients underwent resection, one transplantation and six exploratory laparotomy only.

The surgical mortality rates were 5 per cent for liver resection, 21 per cent for transplantation and 10 per cent for exploratory laparotomy and surgical palliation, for example hepatojejunostomy and gastroenterostomy.

At the time of follow-up, nine patients presented with tumour recurrence after liver resection, all of whom had

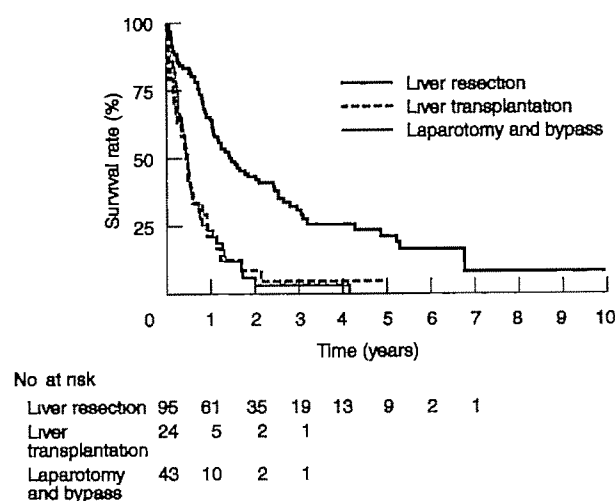


Fig. 1 Survival of patients with cholangiocellular carcinoma according to surgical procedure

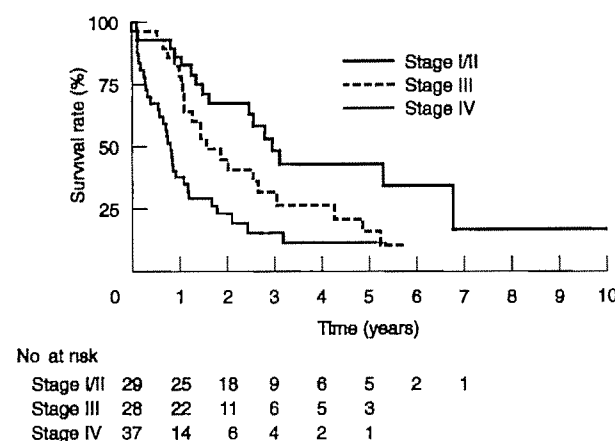


Fig. 2 Patient survival after liver resection for cholangiocellular carcinoma according to Union International Contra la Cancrum tumour stage

local recurrence. Additionally, lung metastases were found in one patient. In the transplant group, only one patient was alive without evidence of tumour recurrence.

Overall survival was 47 per cent at 1 year, 28 per cent at 2 years, 19 per cent at 3 years and 13 per cent at 5 years (median 10.8 months). The respective figures were 64, 43, 31 and 21 per cent (median 17.7 months) for patients who underwent liver resection, and 21, 8, 4 per cent and zero (median 5.5 months) for those who underwent liver transplantation. Patients who underwent exploratory laparotomy only, with or without palliation, had survival rates of 23, 6, 3 per cent and zero (median 5.5 months) respectively

(Fig. 1). Patient survival after liver resection as a function of UICC tumour stage is depicted in Fig. 2.

In 14 patients histological examination revealed components of both HCC and CCC. Serum levels of AFP were available in nine patients with a pathological increase in four. Overall survival was 43 per cent at 1 year, 21 per cent at 2 years, 14 per cent at 3 years and zero at 5 years (median 10.6 months). Survival in 10 patients who had liver resection was 60, 30, 20 per cent and zero (median 13.8 months) respectively. The longest survival time after resection was 58 months. Four patients underwent liver transplantation after which the longest survival was 11 months.

Tumour recurrence, metastases and causes of death

Tumour recurrence and/or metastases were recorded in 50 (53 per cent) of 95 patients after liver resection and in 15 of 24 after liver transplantation. Tumour recurrence in the liver remnant and the graft respectively was observed in 47 patients after resection and in ten after transplantation. After transplantation extrahepatic organ metastases were most frequently found in the peritoneum in four patients, in bone in seven patients, and in lung and pleura in five patients.

Prognostic factors

Univariate analysis identified the following factors with an influence on survival: age, jaundice, liver resection, T, N and M categories, UICC tumour stage, tumour-free surgical margins, vascular infiltration, tumour number, tumour size and serum level of CEA (Table 1). Prognosis was no different in mixed or combined CCC and HCC. Liver cirrhosis was not a prognostic factor in general, but Child B disease had a significant influence in the subgroup of patients with cirrhosis ($P=0.004$). No significance was found for sex, serum level of AFP, Yamanaka type I and II classification, tumour diameter less than 10 cm, less than 5 cm, infiltration of the liver capsule and tumour grade. The medical high-risk factors defined had no prognostic influence.

In the multivariate analysis, the N category (relative risk (RR) 2.05 (confidence interval 1.06–3.98)), M category (RR 3.58 (1.44–8.90)), UICC tumour stage (RR 2.46 (1.71–3.56)) and the presence of jaundice (RR 5.56 (2.16–14.29)) were significant independent prognostic factors.

Discussion

In contrast to HCC, CCC is uncommon, and worldwide experience to date is rather limited. During the past few

Table 1 Univariate analysis of prognostic factors in patients undergoing liver resection ($n=95$) and transplantation ($n=24$) for cholangiocellular carcinoma

Prognostic factor	<i>n</i>	Relative risk	<i>P</i> *
Age (years)			
55	59	0.60 (0.40–0.91)	0.014
>55	60		
Jaundice			
Yes	10	0.37 (0.19–0.73)	0.003
No	104		
Missing	5		
Surgical procedure			
Resection	95	2.97 (1.82–4.82)	0.001
Transplantation	24		
T category			
T ₁₋₃	71		
T ₄	47	3.02 (1.98–4.82)	0.001
Missing	1		
N category			
N ₀	89		
N ₁	30	2.02 (1.27–3.20)	0.002
M category			
M ₀	107		
M ₁	12	2.09 (1.07–4.05)	0.027
Tumour stage			
I–III	63	1.77 (1.43–2.19)	0.001
IV	55		
Missing	1		
Resection margin			
R ₀	99	2.07 (1.20–3.57)	0.008
R ₁₋₂	18		
Missing	2		
Vascular infiltration			
Yes	29	1.87 (1.19–2.93)	0.008
No	85		
Missing	5		
Tumour number			
Solitary	62	1.88 (1.23–2.87)	0.003
Multiple	54		
Missing	3		
Tumour extension			
Unilobar	73	2.41 (1.57–3.70)	0.001
Bilobar	43		
Missing	3		
Child grade			
A	9		
B	10	4.42 (1.47–13.31)	0.004
CEA serum level			
Normal	56	2.23 (1.05–4.89)	0.031
Raised	10		
Missing	53		

Values in parentheses are confidence intervals. T, tumour; N, node; M, metastasis; CEA, carcinoembryonic antigen. *Log rank test

years several retrospective studies have underscored the value of liver resection^{4,5,7,9,10,22,25–29}. However, tumour staging, in accordance with the UICC classification², was not always performed.

The present results were obtained in a large series and confirm the prognostic influence of liver resection and

negative surgical margins^{4,5,22,25–30}. Furthermore, univariate analysis revealed a more favourable prognosis for solitary, unilobar tumours with neither lymph node invasion nor vascular infiltration. This underscores the prognostic influence of the T, N and M category, and UICC tumour stage. Multivariate analysis revealed an independent prognostic influence of lymph node invasion (N) and distant metastases (M), UICC tumour stage and jaundice according to the Yamanaka type III classification.

In the case of conventionally unresectable tumours, the indication for total hepatectomy and subsequent liver transplantation is controversial. The observation of early tumour recurrence, within the first year of transplantation, suggests a negative impact of immunosuppression on aggressive tumours^{23,31}. Despite some prolongation of survival and a short-term improvement in quality of life in the patients who underwent transplantation, the disappointing results overall and the problem of donor organ shortage has led the authors to exclude patients with advanced CCC from liver transplantation. Casavilla *et al.*⁴ recently described the Pittsburgh experience with 20 transplant patients, nine of whom had undergone an extended 'cluster' procedure. These authors have suggested performing liver transplantation in selected patients with less advanced tumours. The concept of extending the indication for liver transplantation to include even patients with resectable tumours, as proposed by Casavilla *et al.*⁴, is not supported by the present results with resection and conventional liver transplantation.

Experience is even more limited with combined and mixed HCC and CCC, which contain components of both tumour entities. Because imaging reveals no specific features³², a clear diagnosis requires histopathological examination of the resection specimen. In cases with hepatocellular components, biliary differentiation on the basis of immunohistological analysis of cytokeratin expression may lead to a diagnosis even in the absence of mucin production²⁰. Preoperative laboratory findings, with raised CEA or CA19/9 levels in addition to an increased serum level of AFP and hepatitis markers, may be suggestive. After hepatic resection involving 27 tumours of the mixed type, Maeda *et al.*³³ observed a 5-year survival rate that was significantly lower than that of HCC in their series but identical to that of CCC. This is confirmed by the present series, which failed to demonstrate a significant difference in prognosis.

Despite a generally unfavourable outcome, the observation of some long-term survivors, as also reported by others^{4,22,34–36}, may in part be due to early diagnosis of less advanced tumours and also to less invasive slow-growing tumours. This raises the question of whether a certain subgroup with a more favourable prognosis might be

identified. Chen *et al.*³⁷ have recently been able to show that patients with mucin-producing CCC, principally papillary adenocarcinoma, had a significantly better prognosis.

In conclusion, this study confirms UICC tumour staging as a reliable instrument for predicting outcome in CCC. Successful liver resection is a positive prognostic factor in the treatment of CCC. Therapeutic efforts should therefore be directed towards achieving resectability. The present data rule out transplantation as a treatment option for advanced unresectable CCC. New criteria must be developed to identify patients with a good long-term prognosis.

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Molecular changes in extracellular matrix turnover after renal ischaemia–reperfusion injury

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Background: Renal ischaemia–reperfusion (IR) injury is an inevitable consequence of transplantation and contributes to later graft fibrosis. This study aimed to elucidate the possible mechanisms by studying the expression of genes associated with extracellular matrix (ECM) turnover.

Methods: Male Wistar rats underwent laparotomy, clamping of the right renal pedicle for 45 min, and left nephrectomy. Control animals underwent left nephrectomy only, or had no operation. Animals were killed at 8, 16 and 24 weeks and messenger RNA was extracted from renal tissue. Genes of interest were amplified and then quantified in an enzyme-linked immunosorbent assay system with levels expressed as a ratio to a known housekeeping gene (*GAPDH*).

Results: Experimental animals developed progressive proteinuria from 16 weeks onwards. At 8 weeks after IR injury, gene levels of matrix metalloproteinase (MMP) 2, an ECM-degrading enzyme, were significantly increased. Levels then fell progressively. This was associated with increasing expression of tissue inhibitor of metalloproteinases (TIMP) 1, an inhibitor of MMP-2, and of transforming growth factor (TGF) β , a profibrotic cytokine, by 24 weeks following injury.

Conclusion: These results suggest that, after an initial phase of increased ECM turnover following IR injury, the balance turns towards one of reduced degradation. This is likely to be an important mechanism in the subsequent development of fibrosis.

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Introduction

Ischaemia–reperfusion (IR) injury to the kidney is an inevitable part of transplantation. As well as immediate deleterious effects, there is no doubt that the endothelial activation and cytokine upregulation associated with ischaemia and reperfusion can also have significant long-term consequences, the major histological manifestation being graft fibrosis^{1,2}.

Although the mechanisms underlying renal fibrosis are complex, a combination of two processes is involved: decreased degradation of the existing extracellular matrix (ECM) and increasing synthesis of ECM components. Matrix degradation involves several enzyme systems, among the most important of which are the matrix metalloproteinases (MMPs)³. One of these (MMP-2) has been shown to be responsible for ECM degradation by mesangial cells *in vitro*⁴. The MMPs have their own specific inhibitors, the tissue inhibitors of metalloproteinases

(TIMPs), and a number of experimental models of renal fibrosis have now reported increased levels of TIMPs, particularly TIMP-1^{5–7}. The cytokine transforming growth factor (TGF) β is known to play an important part in the development of fibrosis and has been shown to stimulate matrix protein synthesis^{8,9}. It also indirectly prevents matrix degradation by increasing production of TIMPs¹⁰.

The changes in ECM dynamics after renal IR have not previously been studied. In the present experiment this was attempted by measuring changes in the messenger RNA (mRNA) expression of TGF- β , the matrix protein collagen III, MMP-2 and TIMP-1.

Methods

Animal model

Male Wistar rats weighing 300–350 g were used in these experiments, which were performed in accordance with

Home Office regulations. Animals were housed three to a cage and allowed free access to standard rat chow and tap water. Animals were anaesthetized by halothane inhalation and the kidneys were exposed via a midline laparotomy. In the experimental group ($n = 6$ per timepoint) the right renal pedicle was exposed with minimal dissection and occluded with a Diffenbach vascular clamp (Bolton Instruments, Bolton, UK). A left nephrectomy was performed. After 45 min of renal ischaemia the clamp on the right kidney was released. This has previously been found to be the longest period of renal warm ischaemia compatible with survival¹¹. Control animals underwent left nephrectomy only; in order to avoid excessive use of animals in this preliminary study, only four rats were used per timepoint. After recovery, animals were returned to their cages and groups were followed for intervals of 8, 16 and 24 weeks. A non-operated control group ($n = 6$) was also studied for baseline values and was simply followed for 24 weeks.

At the appropriate time point animals were anaesthetized, the abdominal aorta was cannulated at laparotomy and the animal killed by exsanguination. The right kidney was removed immediately and tissue strips consisting of the entire thickness of cortex were individually snap-frozen in liquid nitrogen and stored at -70°C until mRNA analysis. Blood was saved for subsequent analysis of serum creatinine levels.

Assessment of renal damage

Proteinuria was used as an indicator of renal damage, and this was assessed at 4-week intervals. Because of the imprecision associated with 24-h urine collection, random urine samples were collected, with the rats housed in metabolic cages for a period of 2–4 h. This caused little disturbance to the rats and allowed them to be denied food for this interval, minimizing contamination. Urine samples were frozen at -20°C until analysis. Urinary total protein (mg/l, determined by the Bradford method¹²) and urinary creatinine ($\mu\text{mol/l}$) were measured on a Beckman Synchron autoanalyser (Beckman Instruments, High Wycombe, UK). This allowed calculation of the urinary protein : creatinine ratio, which has been shown to correlate well with 24-h urinary protein levels, and indeed reflects subsequent renal dysfunction more accurately¹³.

Extraction and quantification of messenger RNA

Details of the methods used in mRNA extraction and reverse transcriptase–polymerase chain reaction (RT-PCR) have been described previously¹⁴. Briefly, samples of renal cortex were homogenized in lysis binding buffer and mRNA was extracted using Dynabeads (Dynal, Bromborough,

UK). mRNA was then converted to complementary DNA by the enzyme reverse transcriptase and subsequent amplification of each gene of interest was performed by PCR. In this preliminary study four genes were chosen: TGF- β , collagen III, MMP-2 and TIMP-1. To allow for differences in cellularity between specimens, the house-keeping gene *GAPDH* was also amplified. All primers were designed using sequences obtained from the European Molecular Biology Laboratories (EMBL) database, using the computer program GCG prime (Genetics Computer Group, Madison, Wisconsin, USA). Quantification of RT-PCR products was performed in an enzyme-linked immunosorbent assay system as described previously¹⁴, with the modification that probes were labelled with digoxigenin¹⁵. Values for genes of interest were calculated as a ratio to the expression of *GAPDH* in the same sample, and expressed in arbitrary units.

Statistical analysis

Mean values of protein : creatinine ratio and gene expression at each timepoint were compared with Student's *t* test for independent samples. Correlation analysis was carried out with the Pearson correlation coefficient.

Results

All the operated animals lost weight in the first week after laparotomy. After this, weight increased steadily and there was no significant difference between the groups. Proteinuria measured by protein : creatinine ratio increased significantly in the experimental animals from 16 weeks onwards compared with values in both control groups (Fig. 1). Serum creatinine concentration at time of death was within the normal range in both experimental and control

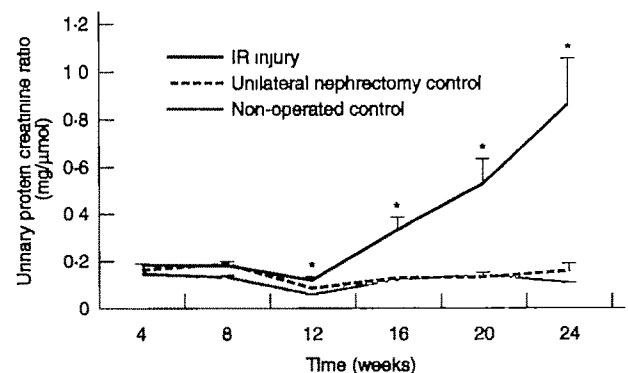


Fig. 1 Proteinuria after renal ischaemia–reperfusion (IR) injury. Values are mean(s.e.m.). * $P < 0.05$ versus both control groups (Student's *t* test)

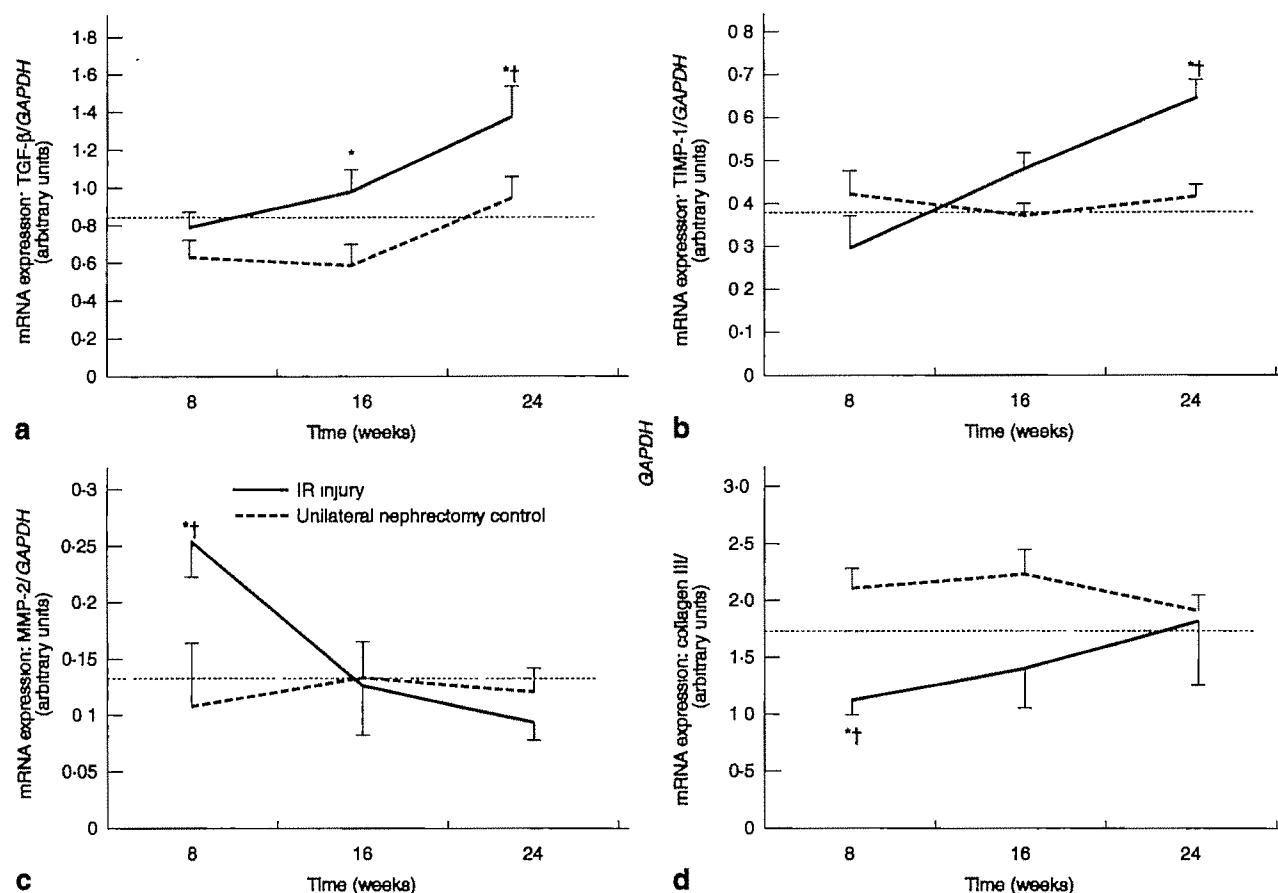


Fig. 2 Messenger RNA (mRNA) expression of fibrosis-associated genes after renal ischaemia-reperfusion (IR) injury. **a** Transforming growth factor (TGF) β ; **b** tissue inhibitor of metalloproteinases (TIMP) 1; **c** matrix metalloproteinase (MMP) 2; **d** collagen III. Values are mean (s.e.m.); horizontal line represents the mean of the baseline group. * $P < 0.05$ versus unilateral nephrectomy group; † $P < 0.05$ versus baseline (Student's t test)

animals and did not differ significantly between them (data not shown).

Gene expression

Levels of mRNA expression for the genes studied are shown in Fig. 2. All levels are ratios of the gene of interest compared with *GAPDH*. TGF- β levels in animals subject to IR injury were significantly increased compared with unilateral nephrectomy controls at 16 weeks; the latter actually had a fall in TGF- β compared with baseline non-operated animals. By 24 weeks TGF- β levels were greater in the experimental group than in either control group. The rise in TGF- β concentration was mirrored by a similar rise in the levels of TIMP-1. In contrast, MMP-2 levels were high after IR injury at 8 weeks and then fell sharply so that they were below control values at 24 weeks. Collagen III levels fell initially in the experimental group compared with controls, and were subsequently at baseline levels by 24 weeks.

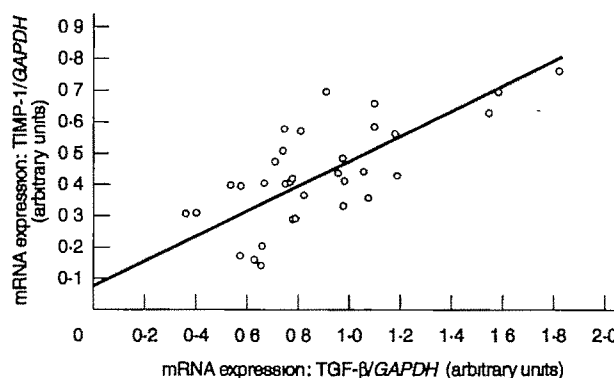


Fig. 3 Correlation of tissue inhibitor of metalloproteinase (TIMP) 1 and transforming growth factor (TGF) β messenger RNA (mRNA) in individual animals. $r^2 = 0.49$, $P = 0.0001$

On an individual animal basis, TIMP-1 mRNA expression correlated strongly to that of TGF- β (Fig. 3). There

was also a correlation between TIMP-1 and collagen III expression ($r=0.456$, $P=0.008$), and a weak inverse correlation with expression of MMP-2 ($r=-0.364$, $P=0.038$). There was no significant correlation between collagen III or MMP-2 mRNA expression and that of TGF- β .

Discussion

This study has shown that 45 min of warm renal IR injury associated with contralateral nephrectomy causes renal damage in the form of proteinuria that is associated with alteration in expression of important genes involved in ECM turnover. Specifically there seem to be two phases after injury. Initially the balance of ECM turnover seems to be in favour of degradation associated with increased MMP-2 and decreased collagen synthesis. Then, by 16 weeks and beyond, when proteinuria becomes evident, increases in mRNA for TGF- β and TIMP-1 suggest that ECM degradation becomes inhibited and the balance tends towards fibrosis.

The finding of an initial phase of increased ECM degradation has not previously been reported in models of chronic renal disease. However, these often involve a more severe injury with florid fibrosis being apparent within a few weeks, and so an initial increase in degradation may have been missed. One of the advantages of the present model is that the changes take place over a fairly long timeframe. Indeed, although not directly comparable, this is a feature of chronic renal fibrosis in humans, including allograft fibrosis. It is easy to envisage that, early after injury, the influx of inflammatory mediators together with degradation of necrotic cells requires a more 'fluid' ECM, and that degradative enzymes are therefore likely to be upregulated in the renal interstitium. MMP-2 may be particularly important as it has high activity against collagen IV or basement membrane collagen³. In the vascular compartment after IR injury endothelial cell damage is associated with migration of smooth muscle cells from media to intima, and this requires breakdown of the internal elastic lamina. MMPs have been shown to have an important role in this process¹⁶. As the mRNA measurement in this study analysed the entire renal cortex, it is not possible to know whether the MMP-2 upregulation was localized to any particular tissue type.

After 16 weeks the increase in TGF- β levels suggests that the balance of ECM turnover has shifted towards accumulation. This corresponds to the beginning of functional deterioration as evidenced by proteinuria. A previous study measuring TGF- β mRNA after warm renal ischaemia in the rat also found that levels increased from 16 weeks onwards².

This was associated histologically with macrophage infiltration and subsequently progressive fibrosis developed. After renal IR injury, TIMP-1, an important inhibitor of matrix-degrading enzymes, is clearly upregulated by 24 weeks after injury, suggesting that decreased ECM degradation is a component in the development of fibrosis at this time. Indeed, levels of one of its main substrates, MMP-2, are decreased, implying an overall swing in the balance of ECM turnover. Similar specific changes in the activity of TIMP-1 and MMP-2 have been demonstrated previously in models of renal⁵ and bladder¹⁷ fibrosis. TGF- β is known to stimulate synthesis of TIMP-1 from fibroblasts and glomerular epithelial cells *in vitro*^{10,18}, and the strong correlation between its expression and that of TIMP-1 in this experiment supports this link.

The role of increased matrix synthesis in the development of fibrosis is less clear. In the present study collagen III was examined and its synthesis was reduced initially and then steadily rose, in proportion to the rise in TIMP-1 concentration, reflecting the change in the dynamics of matrix turnover. Collagen III is just one of many matrix proteins and, although the development of fibrosis after different forms of renal injury has been thought of as a uniform process, subtle variations in the types of matrix protein deposited are likely to be important¹⁹. Hence study of the synthesis of other matrix components is required. Immunohistochemical studies to examine patterns of protein deposition, something not done in this preliminary study, will also be of importance.

Assessment of the effects of IR injury is difficult in humans because of the many confounding variables. Perhaps the nearest situation is in renal transplantation, comparing conventional cadaveric donors with those from non-heart-beating donors (NHBDs) who have suffered more warm ischaemia. When this was done, no differences in TGF- β , MMP-2 or collagen III were found in the first 6 months after transplantation, and levels of TIMP-1 were raised in NHBDs only in week 1²⁰. The main problem in trying to compare this human study with the present experimental data is that several other factors will have influenced gene expression in patients. In particular the effects of brain death and a higher dose of immunosuppressive medication in the conventional group might have negated the effects of increased warm ischaemia in the NHBDs.

Further development of the present experimental model is planned with use of histochemical methods to quantify the development of fibrosis. Longer follow-up will allow a more detailed interpretation of the underlying events, as will the study of additional genes. The upregulation of genes in this model does not prove a causal link with the development of fibrosis. In order to establish this it will be

necessary to administer appropriate inhibitors. There has previously been some success with MMP inhibitors in experimental models of vascular disease²¹.

Despite not being directly applicable to human situations, the experimental model described in this paper does have potential clinical applications. For instance, there are claims that a number of new immunosuppressive drugs for use in renal transplantation are effective in preventing or treating renal fibrosis. This model will provide a relatively simple method for assessing the effect of new drugs on the development of fibrosis. There are also a number of potential methods of manipulating IR injury that have been shown to reduce the initial adverse effects²². With this model, potential long-term benefits of these strategies could be evaluated.

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Effect of colectomy on gastric emptying in idiopathic slow-transit constipation

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Introduction: Gastric emptying is delayed in patients with idiopathic slow-transit constipation (ISTC). Gastric emptying was measured before and after colectomy and ileorectal anastomosis in patients with ISTC to determine whether the abnormality persists after operation.

Methods: Twelve patients undergoing colectomy for severe ISTC had solid-phase gastric emptying measured after an overnight fast. All 12 had an uncomplicated subtotal colectomy and ileorectal anastomosis; 11 had an excellent functional outcome. In ten of these patients gastric emptying was repeated within 3 months of operation. Seven patients (including the remaining two) had the study performed at 1 year.

Results: All 12 patients had severely delayed gastric emptying before operation. Gastric emptying remained delayed in the ten patients who underwent an early postoperative gastric emptying study. Six of seven patients assessed at 1 year had improved gastric emptying, of whom four had returned to normal. Functional outcome did not relate to gastric emptying.

Conclusion: Patients with ISTC have delayed gastric emptying. In some patients this returns to normal after colectomy, but is persistent in others. This may have implications for our understanding of ISTC.

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Introduction

Idiopathic slow transit constipation (ISTC) is a poorly understood disorder of colonic function which occurs predominantly in young women and is characterized by a life-long history of infrequent bowel motions, absence of the call to stool, abdominal bloating and pain^{1–3}. In addition to colonic inertia, there is increasing evidence that patients with ISTC have motility abnormalities of the upper gastrointestinal tract including delayed gastric^{4,5} and gallbladder⁶ emptying, prolonged small bowel transit⁴ and abnormal ileal motility⁷.

It is not known whether these upper gastrointestinal abnormalities are a component part of a pan-gastrointestinal tract abnormality in ISTC or an epiphenomenon secondary to colonic inertia, as it has been shown in animals and humans^{8,9} that inflation of a balloon in the rectum inhibits the entire gastrointestinal tract.

In this study gastric emptying was compared before and after subtotal colectomy and ileorectal anastomosis in patients with ISTC to determine whether the abnormal gastric emptying persists after operation.

Patients and methods

Twelve patients undergoing surgical treatment for severe ISTC were studied. These patients all fulfilled the criteria for surgical intervention to treat ISTC at this institution¹⁰. These include, in the clinical history, life-long constipation, the absence of the call to stool, no aetiological or precipitating factor, and the absence of pain as a predominant feature. None of these patients had an apparent metabolic or endocrine disorder. All patients had failed to respond to prolonged high-dose laxatives and none was using medication for a psychiatric disorder.

On investigation all 12 patients had a normal-calibre colon and rectum on barium enema and delayed colonic transit marker studies (75 per cent of ingested markers remain visible on radiography after 5 days). In addition, the patients were able to evacuate normally on videoproctography (more than 70 per cent of contrast expelled within 30 s).

Before operation, solid-phase gastric emptying was measured after an overnight fast. All laxatives were stopped before the test; all tests were commenced between 09.00 and

10.00 hours. Women underwent the test during the first half of the menstrual cycle. A standard meal of ^{99m}Tc -labelled tin colloid-impregnated filter paper mixed with cornflakes and milk (approximate calorific value 170 kCal) was ingested, and anterior and posterior images were obtained every 2 min for 120 min. The appropriate regions were drawn around the stomach in both anterior and posterior projections from which the geometric mean counts were calculated and plotted against time. Images were examined for evidence of dumping and in each individual a fall in activity was seen to be single exponential. Regression lines were drawn by the method of least squares. Gastric emptying was then expressed as $t_{1/2}$ (the time taken for the count to fall to half the peak value). Where gastric emptying was grossly prolonged, this was recorded as greater than 120 min (the end of the scanning time); these are plotted as 120 min in the figure. Volunteer studies in the authors' department have previously shown that the range of normal for solid-phase gastric emptying is 20–76 min. The results were not corrected for decay of radionuclide. To achieve consistency, four studies (the last four studies performed) reported with correction for decay of the radionuclide were converted to uncorrected counts.

All 12 patients subsequently underwent an uneventful and uncomplicated subtotal colectomy and ileorectal anastomosis. In ten of these patients gastric emptying studies were repeated within 3 months of operation. The remaining two patients failed to attend at that time but underwent a second study at 12 and 18 months respectively. Five of the ten patients who underwent a postoperative gastric emptying study before and early after operation and whose gastric emptying remained abnormal had a third investigation performed 1 year after colectomy.

Results

The study group comprised 11 women and one man; the median age was 33 (range 21–45) years. The median marker retention at 5 days was 89 (75–100) per cent.

All 12 patients had severely delayed gastric emptying before surgery; 11 patients had gastric emptying of at least twice the upper limit of normal (*Fig. 1*). Eleven of the 12 patients who underwent subtotal colectomy and ileorectal anastomosis reported that they had obtained a satisfactory outcome from the operation when reviewed a minimum of 2 years after operation. One patient reported a poor outcome suffering from incapacitating diarrhoea. None of the patients complained of constipation and none required laxatives.

Gastric emptying remained delayed in the ten patients who underwent an early postoperative gastric emptying study (*Fig. 1*), although in two patients a degree of

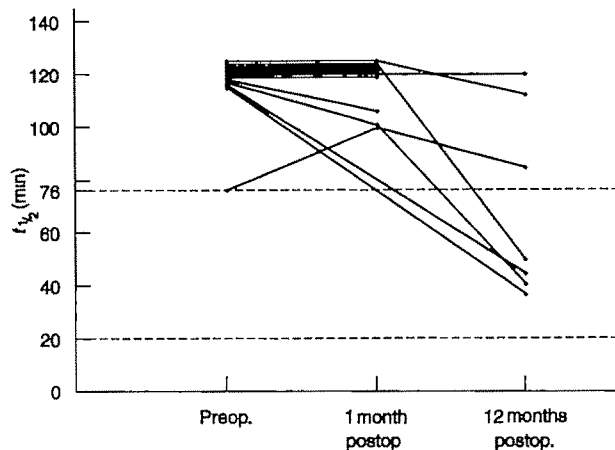


Fig. 1 Solid-phase gastric emptying before, 1 month and 12 months after subtotal colectomy and ileorectal anastomosis in 12 patients with idiopathic slow-transit constipation. $t_{1/2}$ is the time taken for the count to fall to half the peak value. Horizontal dashed lines indicate the normal range

improvement had taken place. Six of the seven patients who were assessed at a later stage had improved gastric emptying. Indeed, this had returned to normal in four patients but remained outwith the normal range in two (*Fig. 1*).

Discussion

The present study confirms that gastric emptying is abnormal in patients with ISTC before surgical intervention. At approximately 1 month after operation, the degree of delay in gastric emptying had not improved in the majority of patients. At 1 year after operation, although the patient numbers are small, there is the suggestion that there may be two groups of patients: those in whom gastric emptying returns to normal and those in whom it remains abnormal.

ISTC is a poorly understood and ill-defined clinical condition of unknown aetiology. Although the disorder characteristically occurs in young women with a life-long history of infrequent stools, absence of the call to stool, abdominal bloating and nausea, several other symptoms are frequently included in the term ISTC. These include patients who attribute the onset of symptoms to childbirth¹¹, hysterectomy¹² or pelvic surgery³. In addition, there are patients whose predominant symptom is that of recurrent straining at stool and tenesmus who have abnormal physiology and/or proctographic findings. It is apparent, therefore, that ISTC is a heterogeneous condition.

There is, however, increasing evidence that patients who attribute the onset of symptoms to hysterectomy or childbirth may have a regional hindgut abnormality with a normal proximal gastrointestinal tract^{11,12}. Further, these patients may respond to a hindgut resection. Patients whose predominant symptoms are those of obstructed defaecation may respond to biofeedback, suggesting the absence of a colonic abnormality¹³. For these reasons, the authors confine the term ISTC to patients who have evidence of delayed transit with normal emptying on proctography. Characteristically this identifies young women with a life-long history. In keeping with other groups^{14,15}, the present authors have found that these patients have a successful outcome with colectomy and ileorectal anastomosis, which contrasts with the poor results obtained by a less selective policy^{16,17}.

The aetiology of ISTC is unknown but it is recognized to be a disorder of colonic motility characterized by a reduction in the frequency, amplitude and duration of propulsive contractions in the large bowel¹⁸. Abnormalities have been shown in the colonic myenteric plexus¹⁹ associated with a functional cholinergic deficit in response to electrical stimulation of the myenteric nerves²⁰. It has recently been suggested that patients with ISTC have a colonic smooth muscle myopathy, which leads to the inability of the surface membrane to initiate and maintain periods of high-frequency spike activity^{18,21}. It is of note in this respect that a similar abnormality has been found in the small bowel in patients with ISTC in whom spontaneous mechanical activity was noted to arise by electrical activity of lower intensity and of shorter duration²². This, in association with the observed delay in gastric and gall-bladder emptying, may suggest that these patients have a pan-gastrointestinal abnormality. There is, however, evidence in both animals and humans that inflation of a balloon in the rectum inhibits proximal gastrointestinal motility and that the avoidance of defaecation has a similar effect^{9,10,23}. It is possible, therefore, that the delay in gastric emptying observed in patients with ISTC before operation may be due to this secondary effect.

It is of interest to note that in the present study there was improvement in the degree of delay in gastric emptying in some but not all patients after colectomy. Indeed, in almost half the patients who underwent the study at 1 year, gastric emptying had returned to normal. These observations may have a number of possible explanations. First, the abnormality may be confined to the lower gastrointestinal tract, with the delay in gastric emptying occurring as a secondary phenomenon due to inertia in the residual rectum. An alternative explanation is that there may be a subgroup of patients with only a colonic abnormality and a further group with both colonic and small bowel myopathies. Finally, it

has been demonstrated that intestinal peptides influence gastric function^{24,25}. Consequently colonic resection, by removing the source of peptides, may inhibit gastric emptying.

In conclusion, this study confirms that patients with ISTC have delayed gastric emptying. The presence of this abnormality, however, did not predict a poor functional outcome after subtotal colectomy and ileorectal anastomosis. Although the delay in gastric emptying improved in the majority of patients after operation, this could take up to 1 year to occur. Further work is required to understand the pathophysiology of inhibition of gastric emptying by constipation.

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Prognostic significance of extensive microsatellite instability in sporadic clinicopathological stage C colorectal cancer

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Background: Colorectal cancers exhibiting microsatellite instability (MSI) appear to have unique biological behaviour. This study analyses the association between extensive MSI (MSI-H), clinicopathological features and survival in an unselected group of patients with sporadic Australian Clinico-Pathological Stage (ACPS) C (tumour node metastasis stage III) colorectal cancer.

Methods: Some 255 patients who underwent resection for sporadic ACPS C colorectal cancer between 1986 and 1992 were studied. No patient had received chemotherapy. Minimum follow-up for all patients was 5 years. Archival normal and tumour DNA was extracted and amplified by polymerase chain reaction using a radioactive labelling technique. MSI-H was defined as instability in 40 per cent or more of seven markers.

Results: Twenty-one patients showed MSI-H. No association was found between MSI and age or sex. Tumours exhibiting MSI-H were more commonly right sided ($P < 0.00001$), larger ($P = 0.002$) and more likely to be high grade ($P = 0.049$). After adjustment for age, sex and other pathological variables, patients whose cancers exhibited MSI-H had improved survival ($P = 0.015$).

Conclusion: Recognition of MSI-H in sporadic ACPS C tumours identifies a subset of cancers with improved prognosis. Such stratification should be considered in trials of adjuvant therapy and may be relevant to therapeutic decision making.

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Introduction

Colorectal cancer remains the second most common cause of cancer-related death in Australia and other Western countries¹, and prognosis continues to be a primary concern of the patient. Despite greater understanding of the molecular events underlying malignant transformation, clinicopathological staging has prevailed as the most reliable indicator of prognosis², the most important prognostic determinants following curative resection being recognized as depth of tumour invasion and nodal status. Within a defined clinicopathological stage, however, length of survival for individual patients can vary widely. This is

most apparent for the 30 per cent of patients presenting with Australian Clinico-Pathological Stage (ACPS) C³ (tumour node metastasis (TNM) stage III) disease for whom 5-year survival is 49 per cent⁴. Additional prognostic stratification would be of value for this large and diverse group of patients and may allow adjuvant therapies to be targeted more selectively.

Microsatellites are tandem repeats of one to six bases found throughout the genome. Microsatellite instability (MSI) (the presence of a novel length allele within a tumour that is absent in the normal tissue)⁵ is a biomarker of deficient mismatch repair, when fidelity of DNA replication is lost. MSI is seen in most tumours occurring in hereditary non-polyposis colorectal cancer (HNPCC)^{6–9}, as well as in 10–15 per cent of sporadic colorectal cancers. Tumours may be subdivided into three groups according to the

The Editors have satisfied themselves that all authors have contributed significantly to this publication.

degree of MSI, those showing extensive marker instability (MSI-high; MSI-H), those showing low levels of instability (MSI-low; MSI-L) and those stable at all markers (microsatellite stable; MSS)⁵.

The MSI phenotype has been reported to have a more favourable prognosis^{6,10–14} but the data have been difficult to interpret because of the use of adjuvant therapy or failure to control for stage. Other studies have failed to show any survival advantage at all¹⁵. This study specifically reviews the prognostic significance of MSI-H in sporadic ACPS C colorectal cancer in patients from a single centre treated by surgery alone.

Patients and methods

Patients

The study population consisted of 281 unselected consecutive patients who had undergone colorectal resection for sporadic ACPS C colorectal cancer between January 1986 and January 1992. All cases were deemed sporadic, based on the absence of relevant family history as recorded prospectively at initial patient interview. Patients fulfilling the criteria of either HNPCC or familial adenomatous polyposis were excluded. None of the patients had received adjuvant chemotherapy and the minimum follow-up for all surviving patients was 5 years.

Twenty-six patients were excluded on the basis of insufficient tissue for analysis, missing sections or lack of correlation between histology reported and section available (25) and a history of perforated tumour at the time of surgery (one), leaving 255 patients for study (197 males and 58 females). In five patients the cancer analysed was a metachronous tumour. Data and histology on the original tumours were unavailable in these cases for comparison. Twenty-five of the 255 patients underwent urgent surgery, for obstruction in 19, bleeding in one and peritonitis in five.

During the study period a uniform surgical management protocol was in place. Clinical data collection was the responsibility of one surgeon (P.H.C.). One pathologist (R.C.N.) performed more than 90 per cent of the specimen dissections and reported on all histology. Tumours were staged according to the modified ACPS system⁴. ACPS C disease is approximately equivalent to TNM stage III disease¹⁶.

Ethical approval for the study was obtained from the institutional review boards of the relevant centres.

Microsatellite analysis

Normal and tumour DNA was extracted separately from paraffin-embedded tissue for each patient¹⁷ and DNA was

amplified by polymerase chain reaction using a radioactive labelling technique¹⁸. A panel of seven microsatellite markers was utilized comprising three mononucleotide repeats (BAT25¹⁹, BAT26¹⁹, c-myb²⁰), three dinucleotide repeats (D5S346²¹, D2S123²², D17S250²³) and one complex tetranucleotide repeat (MYCL²⁴). These markers include the recommended reference panel for the detection of MSI proposed at the National Cancer Institute collaborative meeting on MSI in colorectal cancer⁵. Loci were scored according to the guidelines published.

Based on recent literature a case was designated as MSI-H if instability was seen at 40 per cent or more of the panel of markers²⁵. If one or more of the seven loci were non-informative, the case was scored MSI-H only if there was a 40 per cent or greater instability rate among the remaining markers, provided that a minimum of five had amplified. For the purposes of this study MSS and MSI-L cases were considered together as current literature fails to suggest a clinical relevance for subdivision of this group¹⁴.

Statistical analysis

Contingency tables and the χ^2 test were used to evaluate differences between percentages. Duration of survival was measured from the date of resection until the date of death from any cause or until the censoring date of 31 January 1999. Differences in survival were assessed by the Kaplan–Meier method²⁶ and log rank test, and multivariate models were examined using Cox proportional hazards regression, as implemented in the Egret statistical package²⁷ (Statistical and Epidemiological Research Corporation, Seattle, USA). The appropriateness of the proportional hazards assumption was assessed graphically. Mortality rate ratios were used to assess the difference in deaths due to colorectal cancer. The significance level was set at 0.05 and confidence intervals were at the 95 per cent level.

Results

Twenty-one (9 per cent) of 238 informative cases showed MSI-H. The percentage of markers showing instability in the MSI-H cases ranged from 40 to 100 (mean 67) per cent.

Consistent with the findings of other studies, MSI-H was more likely to be displayed by tumours located in the right colon than those in the left colon or rectum ($P < 0.00001$) and by larger tumours ($P = 0.002$) (Table 1). No association was found between microsatellite status and sex or age. The age of the youngest patient with MSI-H was 65 years; the mean age of this group was 73 years compared with 69 years in the remainder.

Overall survival was significantly greater for patients whose tumours were MSI-H ($P = 0.05$) (Fig. 1). Patients in

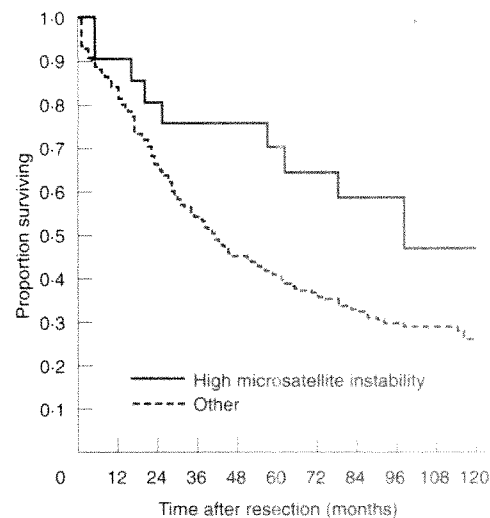
Table 1 Extensive microsatellite instability by clinical and pathological characteristics

	<i>n</i>	No. with MSI-H	<i>P</i>
Sex			0.99
Male	181	16 (9)	
Female	57	5 (9)	
Age (years)			0.23
30–74	174	13 (7)	
75–99	64	8 (12)	
Site			<0.00001
Caecum to transverse colon	65	16 (25)	
Splenic flexure to sigmoid	60	2 (3)	
Rectum	113	3 (3)	
Size			0.002
≤ 4 cm	111	3 (3)	
≥ 4 cm	127	18 (14)	
Direct spread beyond muscularis propria			0.28
No	29	1 (3)	
Yes	209	20 (10)	
Involvement of free serosal surface			0.19
No	204	20 (10)	
Yes	34	1 (3)	
Apical node			0.89
No	228	20 (9)	
Yes	10	1 (10)	
Venous invasion			0.50
No	166	16 (10)	
Yes	72	5 (7)	
Grade			0.049
Low/average	169	11 (7)	
High	69	10 (14)	

Values in parentheses are percentages. MSI-H, extensive microsatellite instability

the present study were a subset of a total of 579 patients with lymph node metastases described previously²⁸. In that study multivariate analysis of a number of pathological variables showed significant independent negative effects on survival from apical node involvement, direct spread beyond the muscularis propria, involvement of free serosal surface, venous invasion, high grade and location in the rectum, after adjustment for age and sex. In the present study the only significant association between MSI and these pathological variables was that high-grade tumours were more likely to display MSI-H.

When the multivariate analysis described previously²⁸ was repeated on the present patients with inclusion of MSI, after adjustment for age and sex, significant negative effects on survival were found for involvement of an apical node, high grade and venous invasion and a significant protective effect for MSI-H. The hazard ratio for MSI-H cancers relative to other cancers was 0.44 (95 per cent confidence interval 0.23–0.85) ($P = 0.015$) (Table 2). The effects noted



No. at risk

High microsatellite instability	21	19	17	16	16	13	11	7	5	4	2
Other	217	183	145	118	98	87	71	55	41	33	26

Fig. 1 Overall survival in relation to microsatellite instability**Table 2** Multivariate survival analysis

	Hazard ratio	<i>P</i>
Microsatellite instability	0.44 (0.23–0.85)	0.015
Apical node	2.29 (1.05–4.98)	0.036
High grade	1.72 (1.22–2.43)	0.002
Venous invasion	1.70 (1.23–2.35)	0.001
Age ≥ 75 years	2.10 (1.50–2.95)	0.001
Male	1.68 (1.12–2.53)	0.013

Values in parentheses are 95 per cent confidence intervals

previously from location in the rectum, direct spread beyond the muscularis propria and involvement of a free serosal surface were not present.

The difference between the number of MSI-H cases and the remainder undergoing urgent surgery was not statistically significant ($P = 0.4$). Of the 176 patients known to have died, the cause of death was established in 149, 92 of whom died from their cancer. Although patients with MSI-H had approximately one-third the risk of dying from their cancer, this difference was not statistically significant.

In this series c-myc and BAT26 demonstrated the greatest sensitivity of the seven markers in detecting MSI-H cases (90 and 86 per cent respectively) and the greatest specificity (99 and 100 per cent respectively).

Discussion

The most important determinant of patient outcome following diagnosis of colorectal cancer is the stage of

disease at the time of treatment. Following curative resection, patients with ACPS A or B (stage I or II) disease have a survival expectation approaching that of the general population, except a small group of male patients with ACPS B disease in which clinical variables such as postoperative complications, urgent surgery and stoma formation, as well as the pathological demonstration of serosal invasion by tumour, independently adversely affect outcome²⁹. Patients with ACPS D/stage IV tumours universally have a poor outcome. The widest variation in survival occurs in patients whose tumours are classified as ACPS C/stage III on current clinicopathological criteria. The benefit of additional information that could reliably discriminate between a tumour with an unfavourable prognosis as opposed to one with a more favourable outcome in this large and prognostically diverse group is evident. This study demonstrates the value of MSI status in this regard. Sporadic ACPS C/stage III colorectal cancers exhibiting MSI-H were associated with significantly improved survival, independently of other pathological variables, compared with tumours that were MSS or MS-L.

The significant association found between sporadic ACPS C/stage III MSI-H colorectal cancers and right-sided location, larger size and improved survival confirms the current view that MSI-H tumours form a biologically distinct group.

The association of MSI-H tumours with mucin production and poor tumour differentiation^{18,30,31}, generally viewed as aggressive histological features, appears to be at odds with the survival benefit MSI-H status confers to the patient. One possible explanation is that the increased level of tumour-infiltrating lymphocytes and expansive (rather than infiltrative) growth pattern, also found in association with these tumours, counterbalance the more aggressive features and reflect a heightened immunological response¹⁸.

The prognostic role of other molecular markers implicated in carcinogenesis has been reviewed extensively^{32,33}. Cancers exhibiting MSI have been shown to be associated with diploid status³⁴ and, in addition, an inverse relationship exists between MSI and rates of loss of heterozygosity (LOH) of DCC/18q and 17p/p53, and the rate of K-ras mutations^{30,35,36}. It is interesting to propose that the reported association between aneuploidy, LOH 18q, LOH 17p and K-ras and worse prognosis in patients is simply a reflection of the surrogate role these markers play in characterizing MSS/MSI-L colorectal cancers as opposed to MSI-H cancers.

Current routine clinical practice offers patients with ACPS C/stage III colorectal cancer adjuvant chemotherapy because of the documented survival benefit it confers on this group³⁷. *In vitro* studies have demonstrated resistance to

many standard chemotherapeutic agents, including alkylating agents, cisplatin, doxorubicin and 5-fluorouracil, in mismatch repair-deficient cell lines^{38–40}, although improved survival in patients with deficient mismatch repair treated with adjuvant chemotherapy has been reported recently^{13,14}. Identification of MSI status will not only impact on the prognostic information a patient receives but may well allow more selective targeting of adjuvant therapy, not only with respect to who will benefit most but also the type of agent used.

In conclusion, sporadic ACPS C/stage III colorectal cancers with MSI-H appear to be a subgroup with distinct unique biological behaviour. They tend to be right sided and larger than MSS colorectal cancers, and are more likely to be high-grade tumours. This unique biological behaviour is associated with a more favourable prognosis independent of other pathological variables. Consideration should be given to determining the MSI status of ACPS C/stage III colorectal cancers because of the valuable prognostic information this provides to both patients and their physicians, and because it may impact on subsequent clinical management.

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Vertical reduction rectoplasty: a new treatment for idiopathic megarectum

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Background: The aetiology of idiopathic megarectum is unknown and the results of surgery are often unsatisfactory. Rectal hyposensation is common and poor perception of rectal filling may contribute to the poor evacuatory function. By reducing the capacity of the rectum, it was hypothesized that sensory thresholds to rectal distension and perception of urge to defaecate would be improved.

Methods: Vertical reduction rectoplasty (VRR) and concomitant sigmoid colectomy was performed on six patients with idiopathic megarectum. Patients were evaluated before and after operation by detailed questionnaire and anorectal physiology. Postoperative rectal compliance was also studied by means of a programmable electronic barostat. Where appropriate, physiological data were compared with those obtained in eight healthy volunteers.

Results: Bowel frequency increased from a preoperative median of 2.5 to 16 per month after operation. Four patients reported improved rectal perception of the urge to defaecate. Thresholds for defaecatory urge and maximum tolerated volume were significantly reduced following VRR ($P < 0.05$). Post-VRR rectal compliance was no different from that in healthy volunteers. Colonic transit time decreased significantly after VRR ($P < 0.05$) and evacuation on proctography increased from a median of 30 per cent to 50 per cent. At a median of 57 weeks' follow-up five of the six patients expressed continued satisfaction with the results.

Conclusion: VRR is a new approach to the treatment of idiopathic megarectum. Clinical and physiological studies confirm that it can improve sensory feedback and defaecation. The procedure needs further evaluation as the number of patients undergoing the procedure increases.

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Introduction

Severe non-obstructive constipation associated with rectal dilatation greater than 6.5 cm on a lateral-view contrast enema is known as megarectum¹. The condition may commence at birth, childhood or in adult life. Although psychological associations² have been made, the cause remains unknown. Histopathological studies have suggested abnormalities in the intrinsic enteric innervation and external muscle layer, although results are conflicting^{3,4}. Derangements in the amount and distribution of excitatory and inhibitory neurotransmitters such as calcitonin gene-related peptide, vasoactive intestinal polypeptide and nitric oxide have also been reported^{3,5}.

With the inevitable failure of conservative therapy, many patients are forced to contemplate surgery. Surgical options are limited and results variable. They include subtotal

colectomy with ileorectal anastomosis, rectal excision with coloanal anastomosis, anterior resection, the Duhamel procedure and restorative proctocolectomy^{6,7}.

Rectal distension studies in patients with megarectum reveal increased sensory thresholds and poor perception of rectal fullness⁸. This may be due to either inadequate stimulation of the receptors of the sensory arm or a disorder of the afferent pathways. The exact location of the receptors for the sensory arm of defaecation in humans is unclear. Proposed receptors include the muscle spindle stretch receptors of the pelvic floor muscles and those within the rectal wall⁹. Electrophysiological studies in animals clearly demonstrate the presence of mucosal, muscular, serosal and mesenteric sensors in the rectal wall that respond to mechanical and chemical stimulation¹⁰.

The new vertical reduction rectoplasty (VRR) operation has been devised based on the hypothesis that reducing

rectal capacity in megarectum would restore perception of rectal fullness and improve sensory and bowel function.

Patients and methods

Patients

Between 1996 and 1999, six patients (three women) underwent sigmoid colectomy and VRR for megarectum defined radiologically. All patients suffered from intractable constipation and had failed conservative therapy.

Before operation patients were evaluated by detailed symptom questionnaire, physical examination, sigmoidoscopy, contrast barium enema, standard anorectal physiology, colonic transit studies and evacuation proctography. Symptom questionnaire, anorectal physiology, evacuation proctography and transit studies were repeated a median of 13.5 weeks after ileostomy closure, and post-operative rectal barostat studies were then performed. Hirschsprung's disease was excluded by full-thickness rectal biopsies or by demonstration of a normal rectoanal inhibitory reflex.

Where applicable, physiological data were compared with values obtained in eight normal volunteers (median age 39 (range 30–52) years; seven women). Assessments were made by a research fellow (O.A.F.) who was not part of the operative team.

The study was approved by the East London and City Health Authority Research Ethics Committee. Informed consent was obtained from all participants.

Anorectal physiology

Rectal sensation was examined by both balloon distension¹¹ and measurement of rectal mucosal electrosensitivity¹². Rectal mucosal electrosensitivity was recorded at 14, 12 and 7 cm from the anal verge. Anal mucosal electrosensitivity was similarly measured and values were obtained for high (5 cm from the anal verge), mid (3 cm) and low (1 cm) levels¹³.

Intensity of sensation was measured on a six-point visual analogue scale and expressed as a percentage of the scale¹⁴, while the duration of perception after cessation of the electrical stimulus was measured in seconds.

Anal resting and squeeze pressures were determined with a single-channel water-perfused catheter (Mediplus, High Wycombe, UK) inserted to 5 cm in the anal canal and gradually withdrawn in 1-cm steps by a standard station pull-through technique¹⁵.

Colonic transit was measured with radio-opaque markers; patients were deemed to have a delay in colonic transit if more than 20 per cent of markers were present at 100 h¹⁶.

Evacuation proctography was performed with a semisolid mixture of barium paste and porridge under fluoroscopic screening¹⁷. The proportion of contrast evacuated, the adequacy of opening of the anorectal angle and the presence of anatomical abnormalities were ascertained. The rectal diameter was calculated by measuring the widest transverse diameter above the anorectal angle.

Rectal compliance and tone were studied after operation with an electronic barostat and results were compared with those from healthy volunteers. The rectal balloon was 1 litre in volume, measured 10 cm in length and was made from infinitely compliant polyethylene¹⁸. Phasic 1-min rectal distensions with air in increments of 2 mmHg over a pressure range of 6–32 mmHg were performed at a rate of 38 ml/s. Distensions were interspersed by 1-min intervals when the pressure returned to zero. Rectal compliance was calculated as a gradient of a pressure–volume curve¹⁹.

Surgical technique

The left colon is mobilized in the usual way and the left ureter identified and preserved²⁰. The inferior mesenteric and superior rectal vessels are similarly identified and preserved. The distal sigmoid colon is transected with a linear stapling instrument (TCT 75 mm; Ethicon, Cincinnati, Ohio, USA). The sigmoid colon and most of the descending colon are resected, the splenic flexure having first been mobilized. The rectum is then mobilized posteriorly by dissecting in the presacral space down to the pelvic floor. Similarly the rectum is mobilized anteriorly and laterally down to the pelvic floor during which the 'lateral ligaments' are divided. Great care is exercised during this dissection to identify and preserve the pelvic autonomic nerves. Risk of damage to these nerves is greatly reduced by keeping the superior rectal vessels intact throughout the procedure. After the rectum has been mobilized, a 100-mm TCT linear stapling instrument is applied along the antimesenteric border of the rectum in a vertical direction to reduce its capacity by a half (*Fig. 1*). The instrument is then fired so that the rectum is bisected into anterior and posterior halves (*Fig. 2*). If the rectal wall is exceptionally thick, it may be necessary to oversee the staple line or divide it between clamps and suture it manually. The anterior portion of the rectum is then excised by applying a 60-mm TLH instrument (Ethicon) at right angles to the vertical staple line at its lower limit. The staple lines are then oversewn with a continuous layer of 3/0 polyglyconate sutures.

A coloneorectal anastomosis is then constructed between the proximal stapled end of the narrowed rectum and the proximal descending colon using a 31- or 33-mm circular stapling instrument (*Fig. 2*). The integrity of the suture lines

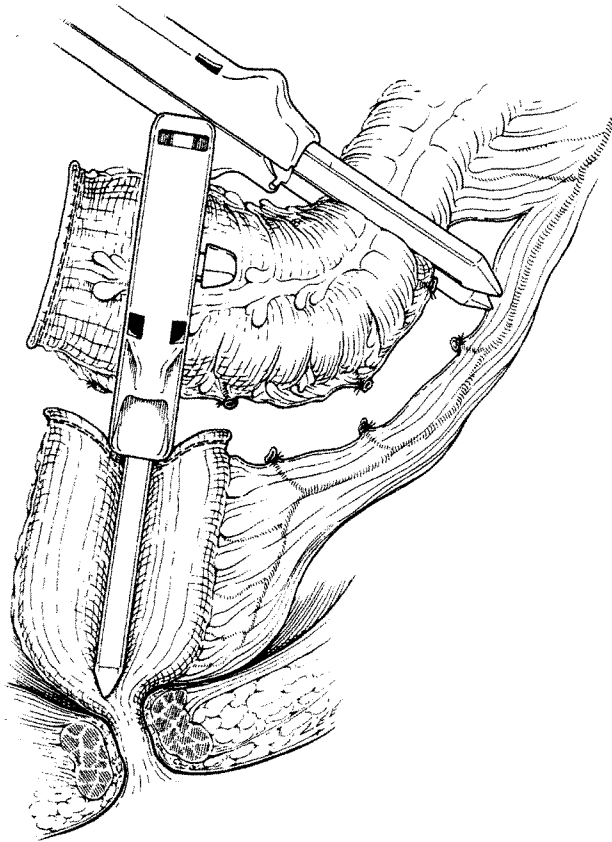


Fig. 1 Vertical reduction of idiopathic megarectum and excision of redundant sigmoid colon with the linear stapling device

is tested by inflating the narrowed rectum with air introduced via a large Foley catheter per anum. Recovery sutures are inserted at any points of leakage until an airtight anastomosis is achieved. A defunctioning loop ileostomy is next constructed in the right iliac fossa and the abdomen is closed.

A water-soluble contrast enema is performed approximately 6 weeks after the procedure. If no leaks are apparent, the loop ileostomy is closed.

Statistical analysis

Non-parametric analysis was by Wilcoxon rank testing for paired data and the Mann-Whitney *U* test for unpaired data.

Results

Clinical

The median age of patients was 32 (range 16–76) years. In three patients symptoms commenced in adulthood; in the

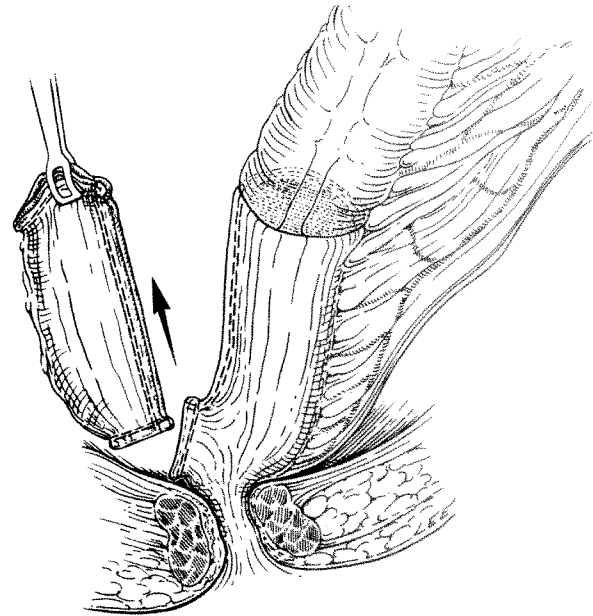


Fig. 2 The anterior half of the rectum is removed after division of its distal connection with the anorectum. The 'vertically reduced' rectum is then anastomosed with the proximal descending colon

other three the history dated from birth. Duration of symptoms was a median of 22.5 (range 3–38) years. Preoperative bowel frequency was a median of 2.5 (1–30) per month. Rectal perception of urge to defaecate was either attenuated or absent in all patients. All patients experienced a feeling of incomplete emptying, abdominal pain, bloating and regularly required assistance in the form of laxatives, enemas or manual evacuation. Minor faecal soiling occurred in five patients.

Following VRR and at a median of 13.5 weeks after reversal of the ileostomy, reported bowel frequency had increased to a median of 16 (4–90) per month. Five of the six patients reported improvement whilst the sixth indicated no change in bowel frequency. Perception of rectal defaecatory urge was restored in four patients who previously had no rectal sensation. Abdominal pain and bloating was ameliorated in four patients. No patient has required regular enemas or digital assistance since the operation. Four patients reported continued intermittent minor faecal soiling, as was present before operation.

Complications included a peristomal infection (one patient), small bowel fistula following ileostomy closure (one) and a short period of postoperative ileus (one). A small radiological leak of the stapled rectum was detected at planned Gastrografin (Schering, West Sussex, UK) enema examination in one patient. The peristomal infection

responded to a short course of antibiotics, and the fistula required surgical excision. The minor anastomotic leak healed with conservative management.

At a median follow-up of 57 (17–91) weeks, five patients expressed continued satisfaction with the results.

Rectal sensation

Before operation all patients had markedly raised rectal sensory thresholds (Table 1). The maximum tolerated volume (MTV) in all patients was over 400 ml. Before VRR the quality of perceived threshold sensations was vague and often perceived in the abdomen or lower back. Following VRR, sensory thresholds were lowered to within the normal range (Table 1). The reduction in median sensory thresholds was significant for defaecatory desire volume (DDV) and MTV (first sensation (FS), $P=0.06$; DDV, $P=0.03$; MTV, $P=0.03$). In addition, the sensations were distinctly perceived rectally.

Table 1 Rectal sensory thresholds before and after vertical reduction rectoplasty

Sensory volume (ml)				
	Preop.	Postop.	Volunteers	P*
FS	262 (30 to >400)	32 (10–74)	14 (5–45)	0.06
DDV	350 (285 to >400)	66 (30–180)	40 (24–65)	0.03
MTV	>400	116 (80–330)	136 (92–168)	0.03

Values are median (range). FS, first perceived sensation; DDV, defaecatory desire volume; MTV, maximum tolerated volume. *Wilcoxon Rank test

Rectal mucosal electrosensitivity thresholds were not measured universally before operation. They were, however, significantly higher at all three levels tested after operation compared with values in volunteers. There was no difference in anal mucosal electrosensitivity thresholds between patients who had undergone VRR and volunteers (Table 2).

The intensity of electrosensation perceived was comparable between all patients following VRR and volunteers in five of six anorectal levels assessed (Table 2). However, at the mid-rectum level the intensity of sensation was significantly higher following VRR than in volunteers ($P<0.05$).

The duration of perceived sensation after cessation of the electrical stimulus was comparable between patients and volunteers (Table 2).

Median post-VRR rectal compliance was 9.7 (range 4.7–32.5) ml/mmHg, which was similar to that of volunteers (10.4 (6.9–20.6) ml/mmHg).

Other anorectal physiology

The median functional anal canal length (3 cm before *versus* 3 cm after operation), resting sphincter pressure (62 cmH₂O before *versus* 94 cmH₂O after operation) and squeeze sphincter pressure (94 cmH₂O before *versus* 117 cmH₂O after operation) were unchanged by operation.

The proportion of retained radio-opaque markers was significantly reduced from a preoperative median of 99 (30–100) per cent to a post-VRR value of 12 (0–74) per cent ($P=0.03$).

The anorectal angle opened normally on evacuation proctography both before and after operation. The amount of evacuated contrast increased from a preoperative median

Table 2 Rectal and anal mucosal electrosensitivity thresholds, intensity of perception and duration of perceived sensation after stopping electrostimulation following vertical reduction rectoplasty and in normal volunteers

	Upper rectum	Mid rectum	Lower rectum	Upper anus	Mid anus	Lower anus
ME threshold (mA)						
Postreduction	22 (13–22)	24 (13–35)	21 (19–35)	12 (3–26)	6 (4–40)	2 (1–7)
Volunteers	5 (3–24)	10 (5–26)	11 (7–24)	12 (1–24)	3 (1–9)	1 (0.7–5)
P*	0.02	0.02	0.02	n.s.	n.s.	n.s.
ME intensity of perception (%)						
Postreduction	20 (0–37)	31 (24–61)	22 (2–47)	44 (8–79)	56 (20–82)	63 (33–85)
Volunteers	12 (4–60)	13 (6–44)	24 (5–65)	40 (5–60)	51 (5–64)	45 (7–63)
P*	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.
Duration of perceived sensation (s)						
Postreduction	3.5 (1–5)	2.5 (1–4)	9 (1–30)	6 (1–14)	3 (2–39.5)	2.5 (1–5)
Volunteers	4 (1–15)	3 (1–35)	4 (1–15)	6.5 (1–30)	2 (1–10)	2 (1–10)
P*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Values are median (range). ME, mucosal electrosensitivity; n.s., not significant. *Mann-Whitney *U* test

of 30 (5–85) per cent to 50 (30–95) per cent following VRR ($n = 5$).

Surgery achieved a reduction in rectal diameter from 12 (10–18) cm before operation to a postoperative value of 6 (5–8.5) cm ($n = 5$).

Discussion

VRR to reduce rectal volume is a new concept in the treatment of megarectum. It has been introduced because of the relatively poor and variable results achieved by more traditional procedures⁷. Colectomy and ileorectal anastomosis, the most common procedure performed, does not address the rectal abnormality and often results in persistent faecal stasis, frequency or incontinence²⁰. Colectomy and caecorectal anastomosis and sigmoid resection may similarly result in persistence of faecal stasis²¹. The Duhamel procedure creates a rectum of even larger volume. As transit through the proximal colon may also be abnormal, the operation rarely succeeds and is associated with high complication rates^{22–24}. Restorative proctocolectomy is a radical procedure with mixed results and a high risk of morbidity²⁵. Rectal excision and straight coloanal anastomosis is open to the same criticisms.

The operation of VRR is based on the concept that most cases of megarectum are associated with a lack of normal rectal sensation. Disturbed rectal sensation and loss of urge to defaecate may occur as a result of pelvic autonomic nerve damage²⁶ and might be sustained during pelvic procedures such as hysterectomy²⁷. In other individuals it might be present from birth, arising from a possible genetic abnormality of sensory neurones²⁸.

Reduction in rectal volume is designed to reduce the amount of distension necessary to trigger those sensory receptors important for normal defaecation and which remain within and without the rectal wall following this procedure. In addition it aims to enhance rectal sensorimotor function by altering compliance towards normality. Previous studies have shown that compliance is increased in megarectum²⁹. Sigmoid resection removes colon that is often dysmotile in these patients and as a consequence is designed to reduce transit time²².

The clinical appraisal by an independent assessor confirmed that the operation was associated with an increased frequency of defaecation, reduction or elimination of the need for manual evacuation and enemas, subjective improvement in rectal sensation, and objective restoration of rectal perception in most patients. Objective assessment indicated that the physiological aims of the procedure were mostly achieved. There was a reduction in all sensory thresholds to rectal distension. In addition, the rectal diameter was reduced, as was colonic transit time.

Evacuatory efficiency was also increased. However, the higher rectal mucosal electrosensitivity thresholds obtained in patients following VRR suggests that some autonomic neuropathy, probably present before operation, may persist in the rectal wall.

It is accepted that the follow-up of these patients is relatively short and that numbers are small, but the findings merit an enlargement of the study. The operation of rectal reduction by vertical rectoplasty may offer a more logical approach to the physiological abnormalities found in these patients than currently available procedures.

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Anal vector volume analysis complements endoanal ultrasonographic assessment of postpartum anal sphincter injury

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Background: The aim of this study was to determine the role of anal vector manometry in the assessment of postpartum anal sphincter injury and to establish the most suitable method of anal vector volume analysis for identifying significant external anal sphincter (EAS) injury in an at-risk parous population.

Methods: A total of 101 consecutive women with a history of instrumental or traumatic vaginal delivery was recruited. Anal ultrasonography and anal vector manometry were performed. Receiver-operator characteristic curves were used to determine the usefulness of anal manometry and anal vector volume analysis in the identification of significant EAS disruption (full thickness, more than one quadrant involved) detected by ultrasonography.

Results: Seventeen women had significant EAS disruption identified by anal ultrasonography. Anal vector manometry provided complementary functional information. Anal vector symmetry index (VSI), determined by analysis of mean maximum squeeze pressure, yielded 100 per cent sensitivity for significant EAS disruption, with a positive predictive value of 61 per cent.

Conclusion: Anal vector manometry complements endoanal ultrasonography. VSI, determined by means of the squeeze pressure profile, correlates best with significant EAS disruption identified at anal ultrasonography.

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Introduction

Anal sphincter injury during childbirth is the most common cause of faecal incontinence in women^{1–3}. The obstetric factors that most expose the anal sphincter mechanism to injury are instrumental delivery and prolonged second stage of labour, particularly during primiparous delivery³. Cumulative injury, particularly to the pudendal nerve⁴, may occur during successive vaginal deliveries, such that an initially occult injury may become symptomatic at the menopause or later when pelvic floor connective tissues atrophy^{4,5}. There is now compelling evidence that women at risk of anal sphincter injury after first delivery should be identified and screened so that cumulative injury may be avoided⁶.

Endoanal ultrasonography has emerged as a useful technique for imaging the anal sphincters and is suitable for screening women for postpartum anal sphincter injury^{7,8}. Used in isolation, endoanal ultrasonography yields no

information regarding anal sphincter function and concern exists that ultrasonography may overdiagnose external anal sphincter (EAS) injuries, particularly in the anterior mid-line^{9,10}. Anal manometry has conventionally been used to assess anal sphincter function^{11–13} but, like ultrasonography, the clinical value of manometry is open to question¹⁴. Conventional anal manometry does not identify segmental anal sphincter injury, which may be both clinically important and amenable to surgical repair. On the other hand, anal vector manometry, which measures radial pressures within the canal, both identifies segmental anal sphincter injury and provides information regarding anal sphincter function^{15,16}. For these reasons anal vector manometry may prove a useful adjunct to ultrasonography in screening women at risk for postpartum anal sphincter injury.

The purpose of this study was to determine the role of anal vector manometry in the assessment of postpartum anal sphincter injury in a large cohort of women at risk of postpartum anal sphincter injury.

Patients and methods

Patients

Between June 1996 and January 1997, a cohort of 101 consecutive women of mixed parity with a history of instrumental or traumatic vaginal delivery was recruited from a dedicated perineal clinic at the National Maternity Hospital, Dublin. All patients were assessed 12 weeks' postpartum by a bowel symptom questionnaire adapted from Pescatori *et al.*¹⁷ to determine a faecal incontinence score, together with anorectal physiology testing which comprised anal vector manometry, anal ultrasonography and assessment of pudendal nerve terminal motor latency (PNTML).

The study was approved by the ethics committee of the National Maternity Hospital, Dublin. All patients gave written informed consent.

Anal manometry

Anal manometry was performed with a lower gastrointestinal manometry system (PC Polygraf HR; Synectics Medical, Stockholm, Sweden) with an eight-lumen vector volume polyvinyl chloride catheter (VMC8; Zinetics Medical, Salt Lake City, Utah, USA). The recording catheter was connected to a pneumohydraulic capillary infusion system (Mui Scientific, Mississauga, Ontario, Canada) and perfused with sterile water at 0.5 ml/min per channel using a perfusion pressure of 80 kPa. Perfusion ports were located 1 cm from the catheter tip and arranged radially at intervals of 45°. The catheter was graduated at 1-cm intervals. Channel 1 was identified by a longitudinal black line along the catheter. Each capillary tube from the eight-lumen catheter was connected to an external PBV transducer (DPT6100; SIMS Medical Systems, Hythe, UK) and data were transmitted to a PC Polygraf with all eight channels set to record manometric data. The recorded data were transferred to an IBM-compatible pentium 120-Hz PC on which the procedure was recorded in real time and stored directly on the hard disk for review and analysis.

Three resting and three maximal squeeze anal canal pressure profiles were obtained for each patient with a 1-min rest between each squeeze profile. Constant radial orientation of the catheter was maintained during each pressure profile. These recorded data were then analysed to determine the mean maximum resting pressure (maxRP), mean maximum squeeze pressure (maxSP) and, by subtraction of these two values, the mean squeeze increment (SI) pressure for the anal canal. The functional length (FL) of the high-pressure zone of the anal canal (greater than 20 mmHg) was determined for both resting and squeeze profiles.

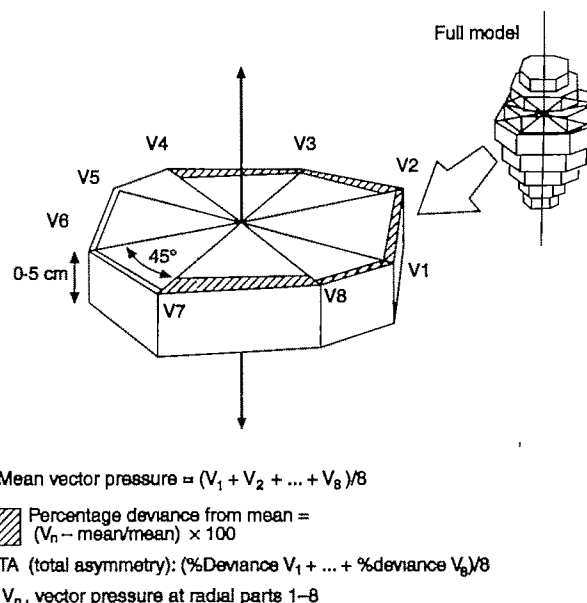


Fig. 1 Technique for assessment of anal vector symmetry using total radial asymmetry. Mean asymmetry of the anal canal is derived from the sum of the differences between the minimum vector volumes and the mean of all vector volumes at each level within the anal canal

Anal vector volume analysis

Analysis of anal canal vector volumes was determined using two separate methods, one to derive total radial asymmetry (TA) and the other a vector symmetry index (VSI). TA was determined with a commercially available software package (Polygram Lower GI, version 6.4; Synectics Medical) (Fig. 1). The calculation used measures the mean asymmetry of the anal canal derived from the sum of the deviances of minimum vector volumes from the mean of all vector volumes at each level within the anal canal. VSI was determined using customized software and the formula described originally by Perry *et al.*¹⁵ for resting (VSI_r) and squeeze (VSI_s) pressures (Fig. 2). This method of calculation divides the anal canal into eight segments, the volume of each being the sum of the vector volumes within each segment. The minimum segment volume is then expressed as a proportion of the maximum segment volume.

Anal ultrasonography

Anal ultrasonography was performed in the left lateral decubitus position using a Bruel and Kjaer 360° 10-MHz rotating transanal endoprobe⁷. This allowed visualization of the internal and external anal sphincters. Anal sphincter injury was scored independently by two radiologists and

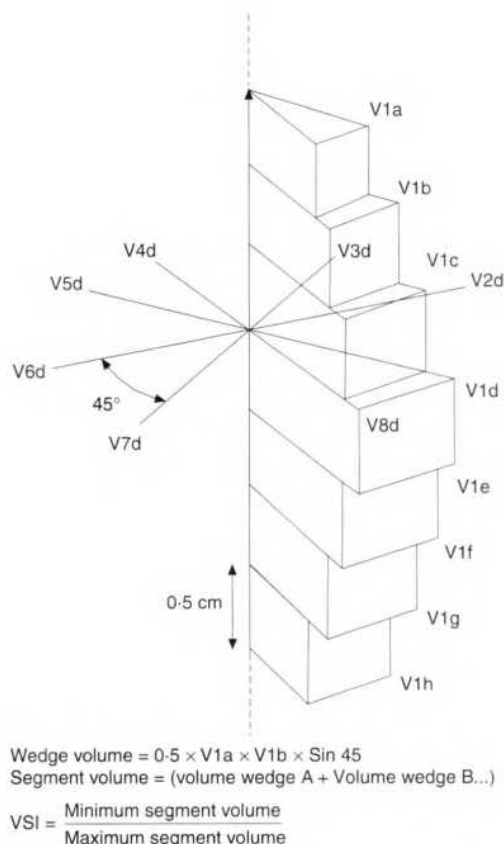


Fig. 2 Technique for assessment of anal vector symmetry index (VSI), where V is vector pressure (mmHg). The volume of each of eight segments in the anal canal is the sum of the vector volumes within each segment. The minimum segment volume is expressed as a proportion of the maximum segment volume

quantified according to the number of quadrants involved and whether the injury was partial or full thickness. Significant EAS injury was defined as full-thickness disruption of the EAS involving at least one quadrant of the anal canal circumference (Fig. 3).

Pudendal nerve terminal motor latency (PNTML) measurement

PNTML was measured using a St Mark's Hospital electrode (Dantec, Skovlunde, Denmark). A stimulus of 50 V for 0.1 ms was delivered at one pulse per second, and the shortest reproducible latency was recorded on an MS91 EMG machine (Medelec, Old Woking, UK). The PNTML was considered prolonged if it was greater than 2.4 ms¹⁸.

Statistical analysis

All data were transferred to an IBM-compatible Access database and statistical analysis was performed for median

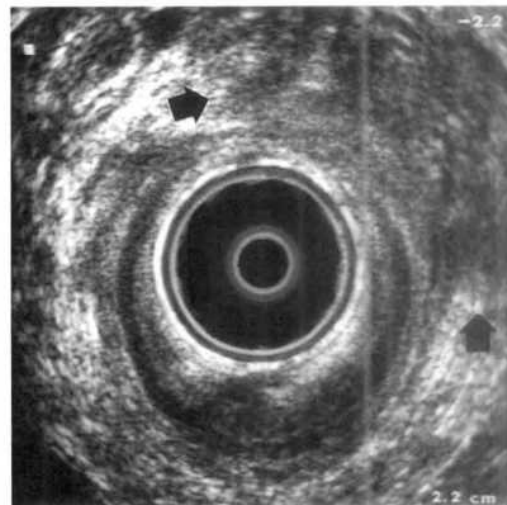


Fig. 3 Endoanal ultrasonography demonstrating significant (full thickness, more than one quadrant) disruption of the external anal sphincter muscle

values using the Wilcoxon rank sum test and Kruskal-Wallis one-way analysis of variance where appropriate, on an SPSS for Windows statistical software package (IBM, Flushing Meadows, New York, USA). The sensitivity, specificity and positive predictive value (PPV) for each technique of anal vector volume analysis used to identify women with significant EAS injury ($n=17$) were determined. Receiver-operator characteristic (ROC) curves were generated using the S-Plus statistical software package (MathSoft, Seattle, Washington, USA) to determine the pair of sensitivity and specificity estimates at each cut-off point, to plot the non-parametric ROC curves by joining these pairs and to estimate summary statistics for the area under the curve¹⁹. Similarly, ROC curves were generated to identify the usefulness of anal vector manometry in detecting women with significant alteration in faecal continence (symptom score greater than 10).

Results

The mean age of women at presentation was 35 (range 21–48) years. Thirty-one women presented following instrumental vaginal delivery, and 70 after primary obstetric anal sphincter repair of a recognized third-degree perineal injury. Eighty-seven women presented after primiparous delivery and 14 following multiparous vaginal delivery.

Symptoms

Forty-three women complained of impaired faecal continence, with a median incontinence score of 9 (interquartile

range (i.q.r.) 6–14). Ten women complained of episodic frank faecal incontinence, 27 of faecal soiling and poor control of flatus, and six of incontinence of flatus only. Twenty-one women complained of faecal urgency of less than 5 min.

Anal ultrasonography

Seventeen women were found to have significant EAS disruption (full thickness, defect of more than one quadrant (90°)) on ultrasonography and 11 had a combined full-thickness defect of the EAS and the internal anal sphincter. Eighty-four women had partial-thickness injury to the EAS or full-thickness injury of less than one quadrant (90°) and constituted a control group against which women with significant injury were compared.

Anal manometry

The results in *Table 1* show that anal manometry parameters were reduced in women with significant EAS disruption ($n=17$) and in those with symptoms of altered faecal continence ($n=43$). The results of anal vector symmetry analysis are given in *Table 2*. Both VSI_r and VSI_s were significantly reduced in women with symptoms of altered faecal continence compared with values in women with no symptoms. By contrast there was no difference in TA

between the two groups. ROC curves for VSI_r , VSI_s and TA (*Fig. 4*) revealed greater areas under the curve for VSI_r and VSI_s than for TA (*Table 3*). ROC curves for maxRP, maxSP and SI pressure did not allow a useful cut-off point to be determined. The sensitivity, specificity and PPV for VSI_r , VSI_s and TA are given in *Table 3* and indicate VSI_s to be the most useful parameter in screening for significant EAS disruption, with 100 per cent sensitivity and a PPV of 0.61 at a median cut-off of 0.44.

The results of anal manometry (*Table 1*) and anal vector volume analysis (*Table 2*) showed significant differences between women with normal continence ($n=58$) and those with symptoms of altered faecal continence ($n=43$). ROC curves generated to determine the usefulness of anal manometry and anal vector volume analysis in identifying women with significant faecal incontinence did not allow useful cut-off points to be determined.

Pudendal nerve terminal motor latency

The mean PNTML value was 2.1 (i.q.r. 1.7–2.6) ms on the right side and 2.2 (i.q.r. 1.9–2.6) ms on the left. Thirteen women had pudendal neuropathy; in nine women this was bilateral. The median SI pressure was lower in women with neuropathy (13.0 (i.q.r. 9.2–18.5) mmHg) compared with that in women with no neuropathy (26.2 (i.q.r. 8.0–49.0) mmHg; $P=0.001$, Mann–Whitney U test).

Table 1 Postnatal assessment of anorectal physiology parameters following traumatic vaginal delivery

	Symptoms ($n=43$)	No symptoms ($n=58$)	P^*	EAS injury ($n=17$)	No EAS injury ($n=84$)	P^*
MaxRP (mmHg)	35.0 (24–54)	43 (30–62.3)	0.04	30 (22–43)	45 (30–62)	0.002
MaxSP (mmHg)	57.4 (45–79)	78 (54–85)	0.01	59 (42–77)	73 (49–89)	0.02
SI pressure (mmHg)	17.4 (9–29)	26 (14–45)	<0.001	26 (9–29)	26 (15–45)	0.05
Functional length (cm)						
Resting	2.0 (1.5–3.0)	2.0 (1.4–3.0)	0.6	1.5 (0.25–2.5)	2.0 (1.5–3.0)	0.06
Squeeze	3.0 (2.0–3.5)	3.5 (2.5–4.0)	0.02	2.5 (1.25–4.0)	3.0 (2.5–4.0)	0.01

Values are median (interquartile range). EAS, external anal sphincter; MaxRP, maximum resting pressure; MaxSP, maximum squeeze pressure; SI, squeeze increment. *Wilcoxon rank sum test

Table 2 Postnatal assessment of anal vector symmetry following traumatic vaginal delivery

	Symptoms ($n=43$)	No symptoms ($n=58$)	P^*	EAS injury ($n=17$)	No EAS injury ($n=84$)	P^*
VSI_r	0.50 (0.35–0.74)	0.61 (0.47–0.79)	0.02	0.29 (0.24–0.37)	0.63 (0.48–0.8)	0.001
VSI_s	0.55 (0.38–0.72)	0.70 (0.48–0.83)	0.001	0.33 (0.29–0.39)	0.7 (0.54–0.83)	0.001
TA	0.43 (0.36–0.49)	0.42 (0.32–0.49)	n.s.	0.47 (0.43–0.5)	0.4 (0.33–0.48)	0.05

Values are median (interquartile range). EAS, external anal sphincter; VSI_r , resting vector symmetry index; VSI_s , squeeze vector symmetry index; TA, total radial asymmetry; n.s., not significant. *Wilcoxon rank sum test

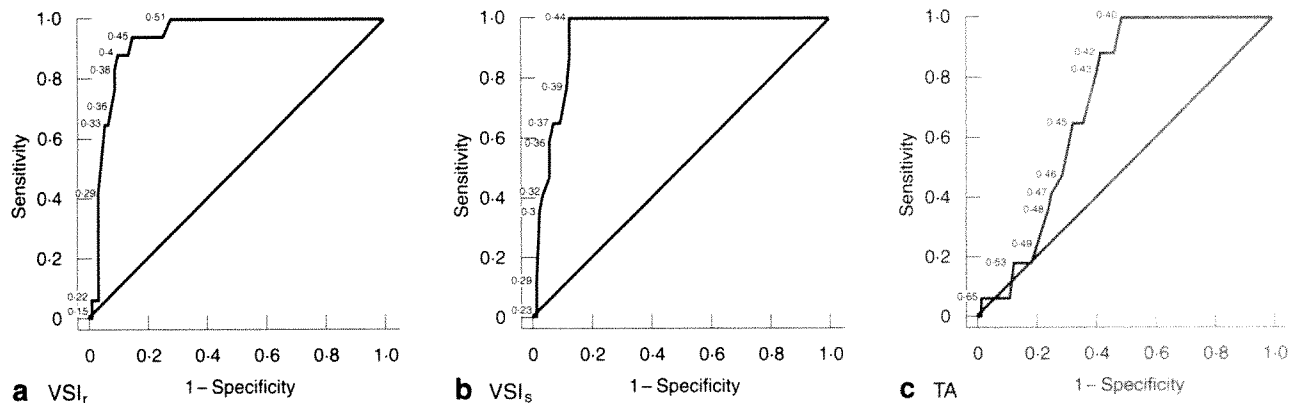


Fig. 4 Receiver-operator characteristic curves for detecting significant postpartum external anal sphincter disruption predicted by a vector symmetry index (VSI) for resting pressures, **b** VSI for squeeze pressures and **c** total radial asymmetry. Values on graphs are median cut-off points

Table 3 Detection of external anal sphincter disruption with anal vector manometry

	Area	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)
VSI _r	0.93 (0.78–0.98)	0.43	88	87	58
VSI _s	0.94 (0.79–0.98)	0.44	100	87	61
TA	0.72 (0.61–0.81)	0.30	88	58	30

Values in parentheses are 95 per cent confidence intervals. Area, median area under receiver-operator characteristic curve; cut-off, median optimum lower limit of normality; PPV, positive predictive value; VSI_r, resting vector symmetry index; VSI_s, squeeze vector symmetry index; TA, total radial asymmetry

Discussion

The anal sphincter is vulnerable to injury during vaginal delivery. Recent work has revealed a high incidence of previously unrecognized anal sphincter injury, which occurs during primiparous vaginal delivery^{1–3,6}. These findings raise issues regarding the obstetrical risk factors underlying such injury and the need to identify, through appropriate postnatal screening, women at risk of cumulative injury to the anal sphincter mechanism during subsequent vaginal delivery^{6,20}.

Endoanal ultrasonography, initially introduced as an adjunct to conventional physiological assessment of anorectal function^{7,8}, has tended to supplant physiological assessment as the optimal technique for assessment of anal sphincter integrity⁷. In part, this change has been brought about by lack of agreement concerning the best method of performing anal manometry^{13–15} and the difficulty of

establishing acceptable ranges of normality in comparable control populations. Commercially available computerized anal manometry systems have proved disappointing in the apparent lack of correlation between ultrasonographic findings and the results of anal manometry¹⁴.

This study examined the role of anal manometry and pudendal nerve assessment in a large cohort of women at risk of persistent anal sphincter injury following parturition. Measurement of anal canal vector volume, determined by quadrantic analysis using the formula derived by Perry *et al.*¹⁵, was found to calculate a VSI with a high sensitivity for identifying clinically significant full-thickness EAS disruption detected by endoanal ultrasonography. In addition, anal manometry provides information regarding anal sphincter function that is not provided by anal ultrasonography alone. This information is clinically important as it can point towards pudendal nerve injury that may occur in the absence of anatomical anal sphincter disruption.

Anal vector volume analysis may be performed in two ways. The VSI analysis defines vector volume in 45° sectors (V1–V8) at 0.5-cm increments (A–H) along the anal canal (Fig. 2). VSI is defined as the ratio of the smallest to the largest sector volume, a ratio that tends to highlight asymmetry. By contrast, TA measurement derives asymmetry from the ratio of smallest radial pressure to the average pressure within the anal canal (Fig. 1). This calculation does not, therefore, take account of the pressure changes on either side of the lowest vector, which are included in calculation of the average pressure. This method of calculation tends to minimize asymmetry, particularly in the presence of a single-quadrant defect, typical of obstetric injury.

One of the most difficult aspects of validating anal manometry as a clinical test is the selection of an

appropriate control population. Anal canal pressures differ between the sexes and with age²¹. Anal canal pressures and VSI are reduced following vaginal delivery, and even more so after instrumental or traumatic delivery³. In this study a parous female population at risk of sphincter injury, including those with and without significant EAS disruption, was investigated. This allowed valid comparison of VSI between those with EAS disruption and those without, drawn as they were from the same population. By using an 'at risk' control population and defining what constituted a 'significant' EAS injury, the pitfall of overdiagnosis of anal sphincter injury has been avoided, a criticism made of anal ultrasonography²².

It is concluded that anal vector manometry, using vector analysis of anal squeeze pressure (VSI_a), is complementary to endoanal ultrasonography as it provides information regarding anal sphincter function as well as verification of anal sphincter disruption. Anal vector manometry is of potential use as an independent method of screening women at risk of anal sphincter injury which might allow adequate counselling and an informed choice regarding the mode of delivery in future pregnancies^{6,19,23}.

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Matrix metalloproteinases, their tissue inhibitors and colorectal cancer staging

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Background: Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are important in tumour invasion and metastasis. The levels of MMPs, TIMPs and total MMP activity were compared in paired colorectal tumour ($n = 50$) and normal tissue ($n = 49$) samples and correlated with clinical and pathological staging.

Methods: Gelatin zymography (MMP-2 and MMP-9), enzyme-linked immunosorbent assays (MMP-1, MMP-3, TIMP-1 and TIMP-2) and quenched fluorescent substrate hydrolysis (total MMP activity) were employed in resection specimens from 50 patients, four with adenomas and 46 with colorectal cancer.

Results: The levels of active MMP-2 and MMP-9 and total MMP-1, MMP-3 and TIMP-1 were significantly greater in tumour tissue than in normal colon (e.g. TIMP-1 tumour median 72 (range 25–351) *versus* normal 26 (4–107) ng per mg total protein content; $P < 0.05$); however, TIMP-2 levels were significantly greater in normal tissue ($P < 0.05$). Total MMP activity was significantly greater in tumour than in normal tissue (15 025 (1750–174 400) *versus* 7250 (750–354 650) $\text{pmol l}^{-1} \text{min}^{-1} \text{mg protein}^{-1}$; $P < 0.05$). Correlations were found between both MMP and TIMP levels and pathological tumour staging. MMP-1 appeared to be most important as its concentration correlated positively with Dukes staging, tumour differentiation and lymphatic invasion.

Conclusion: The levels of the studied MMPs and total MMP activity were upregulated in colorectal tumours. MMP-1 is important in colorectal cancer progression.

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Introduction

Tumour invasion and metastasis involves a complex cascade of events including tumour growth and angiogenesis, local invasion, intravasation, extravasation, and finally growth and survival at a secondary site¹. At each stage of the metastatic cascade, complex and coordinated interactions exist between the tumour and the surrounding tissue (extracellular matrix; ECM) involving many different factors including proteinases, proteinase inhibitors and adhesion molecules.

The proteinases primarily involved in ECM degradation in both normal and pathological processes² are the matrix metalloproteinases (MMPs). The members and properties of MMPs have been reviewed extensively^{3–5}. In normal conditions MMP activity *in vivo* is tightly controlled at several levels, including gene activation and transcription, extracellular activation of secreted latent MMPs and inhibition by tissue inhibitors of matrix metalloproteinases

(TIMPs)⁶. In certain pathological processes, including cancer, MMPs are not normally regulated and the balance in active MMP–TIMP expression may favour proteolysis. As MMPs are involved in ECM degradation at several stages of the metastatic cascade, the levels of these MMPs may be of prognostic significance.

MMP and TIMP expression has been determined previously in colorectal cancer. However, the majority of these studies have determined the expression of individual MMPs^{7–12} or TIMPs^{7,12}, involved only small sample numbers, or failed to correlate the expression of MMPs and TIMPs with pathological staging¹³. These previous studies have sometimes demonstrated conflicting results regarding MMP expression in colorectal cancer which can be explained in part by differences in sample numbers and the application of different techniques¹⁴. Therefore, there is still limited information on the expression, activation and involvement of MMPs in malignant progression of colorectal cancer. This study compared the levels of several

MMPs (the gelatinases (MMP-2 and MMP-9), interstitial collagenase (MMP-1), stromelysin 1 (MMP-3)), total MMP activity and the levels of TIMP-1 and TIMP-2, and correlated their expression with clinical and pathological staging.

Methods

Materials

All materials were purchased from Sigma Diagnostics (Poole, UK) unless stated otherwise.

Tissue samples and protein concentration

Paired colorectal (tumour margin and normal) tissue samples were collected immediately after surgical resection (April 1998 to June 1999). Each tissue sample was finely diced with scalpels, homogenized (Polytron PT 2100; Kinematica, Lucern, Switzerland) and centrifuged at 5000 r.p.m. The homogenate was then stored in aliquots at -80°C until analysis. The total protein concentration of each tissue sample was determined by the method of Ohnishi and Barr¹⁵.

Gelatin zymography

Gelatinases (MMP-2 and MMP-9) were detected by gelatin zymography adapted from Heussen and Dowdle¹⁶. In brief, tissue homogenates were electrophoresed down a 12 per cent sodium dodecyl sulphate gel containing 0.1 per cent gelatin at 200 V for 45 min (Mini-protean plus; Biorad, Hemel Hempstead, UK). Gels were washed, incubated overnight and stained as described previously¹⁷. Control gels were incubated with the MMP inhibitor, ethylene-diamine tetra-acetic acid 10 mmol l^{-1} .

Quantification of gels was performed using densitometry (GS-700; Biorad) linked to Revelation Software (Biorad). The area and optical density of each latent and active gelatinase band were determined for each sample.

Enzyme-linked immunosorbent assay

MMP-1, MMP-3, TIMP-1 and TIMP-2 protein levels were determined by Biotrack enzyme-linked immunosorbent assays (ELISAs) (Amersham Pharmacia Biotech, Little Chalfont, Bucks, UK). Duplicate tissue sample homogenates were diluted where necessary (MMP-1, 1:2; TIMP-1, 1:3) and the ELISA was performed following the assay protocol. The optical density of each well was determined with a microplate reader set at 450 nm linked to Revelation Software to determine antigen concentrations

(Dynatech Laboratories, Billingshurst, UK). Results were expressed as nanograms of antigen per milligram of protein.

Quenched fluorescent substrate hydrolysis

Total MMP activity was determined for each sample by quenched fluorescent substrate hydrolysis (QFSH)¹⁸ using the fluorescent substrate Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂, as described previously¹³. Results were expressed as the rate of substrate hydrolysis ($\text{pmol l}^{-1}\text{ min}^{-1}\text{ mg protein}^{-1}$).

Statistical analysis

For comparisons between MMP and TIMP levels in colorectal tumour and normal tissue samples, the Mann-Whitney *U* test for non-parametric data, with 95 per cent confidence limits, was performed. Spearman's correlation coefficient was used to determine whether a correlation existed between MMP or TIMP level and clinical pathological staging. The χ^2 test was performed to determine differences in the detection of gelatinases between tumour and normal tissue. Differences were considered significant at the $P < 0.05$ level.

Results

Of the 50 patients, four had adenomas, six had Dukes A tumours, 18 Dukes B, 20 Dukes C, and two had distant metastatic disease (Dukes 'D'). Of the 46 tumours, 11 were well differentiated, 28 moderately and six poorly differentiated; 21 had undergone lymphatic invasion and 14 vascular invasion. The tumour differentiation was missing from the histology report for one patient.

Gelatinase expression

Following gelatin zymography, the active forms of both gelatinases (MMP-2 and MMP-9) were detected in a significantly greater number of tumours than in normal colorectal tissue (*Figs 1 and 2*).

There appeared to be a correlation between the detection of active MMP-9 with Dukes stage (*Fig. 2*). For both gelatinases the adenomas demonstrated a lower activity ratio (active:latent bands) than any Dukes staged tumour (data not shown).

Matrix metalloproteinase 1 expression

MMP-1 levels were significantly greater in colorectal tumour than in normal tissue ($P < 0.05$) (*Table 1*). MMP-1 levels in tumour tissue correlated significantly with Dukes

stage ($P < 0.05$, Spearman correlation) (Fig. 3a and Table 2), tumour differentiation ($P < 0.05$) (Fig. 3b) and lymphatic invasion compared with no lymphatic invasion (median 16.3 (range 0.9–52.1) versus 5.7 (0.1–32.3) ng per mg protein; $P < 0.05$). There was also a trend towards increasing MMP-1 levels with increasing tumour depth (from T₁ to T₄).

Matrix metalloproteinase 3 expression

MMP-3 levels were also significantly greater in colorectal tumour tissue than the corresponding normal tissue

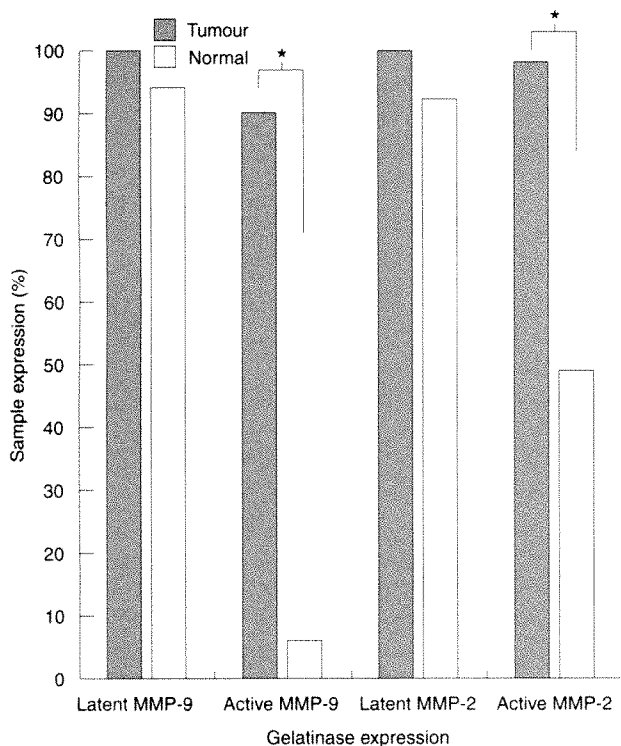


Fig. 1 Percentage of colorectal samples from tumour and normal tissue demonstrating latent and active gelatinase (matrix metalloproteinase (MMP) 2 and MMP-9) lysis bands as detected by gelatin zymography. * $P < 0.05$ (χ^2 test)

($P < 0.05$) (Table 1). Although there was a trend towards increasing MMP-3 levels with Dukes stage, the differences were not significant. MMP-3 and tumour differentiation also showed a positive trend, with poorly differentiated tumours demonstrating higher MMP-3 expression (median 13.1 (1.6–69.1) ng per mg protein) than either well (6.0 (0.6–43.5) ng per mg protein) or moderately (5.9 (0.9–45.0) ng per mg protein) differentiated tumours

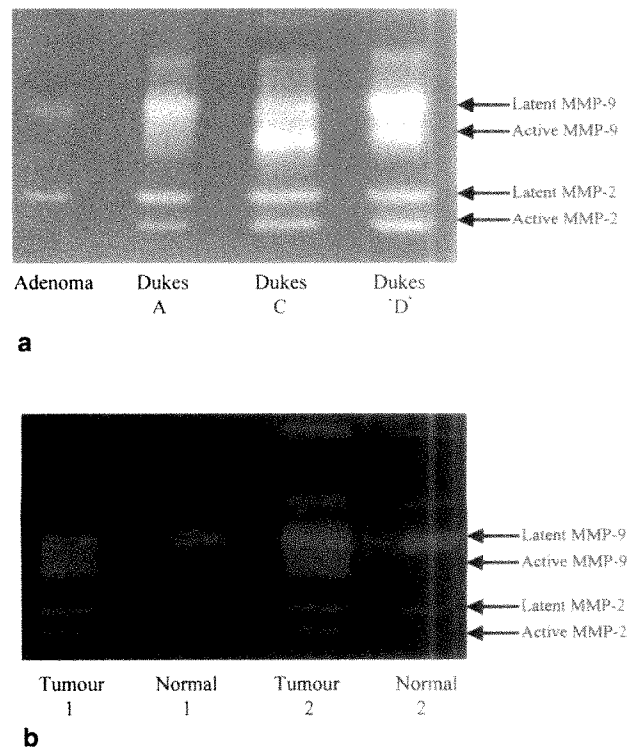


Fig. 2 Representative gelatin zymograms illustrating differences in gelatinase detection (matrix metalloproteinase (MMP) 2 and MMP-9) in **a** different stages of colorectal cancer and **b** two paired tumour and normal tissue samples. The latent forms of MMP-2 and MMP-9 were detected in all tissue samples, but the active forms were present only in tumour tissue of Dukes stage A and above, not in adenomas or normal colorectal tissue

Table 1 Differences in the levels of matrix metalloproteinases and tissues inhibitors of metalloproteinases and total matrix metalloproteinase activity in colorectal tumour and normal tissue

	MMP-1 (ng mg protein ⁻¹)	MMP-3 (ng mg protein ⁻¹)	TIMP-1 (ng mg protein ⁻¹)	TIMP-2 (ng mg protein ⁻¹)	Total MMP activity (pmol l ⁻¹ min ⁻¹ mg protein ⁻¹)
Tumour	7.0 (0.1–52.1)*	6.0 (0.2–69.1)*	71.7 (25.3–351.2)*	2.1 (0–10.4)	15 025 (1750–174 400)*
Normal	0.1 (0–3.8)	1.5 (0.2–57.0)	26.2 (4.4–107.0)	3.4 (0–11.0)*	7 250 (750–354 650)

Values are median (range). MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases. * $P < 0.05$ versus normal tissue (Mann-Whitney *U* test)

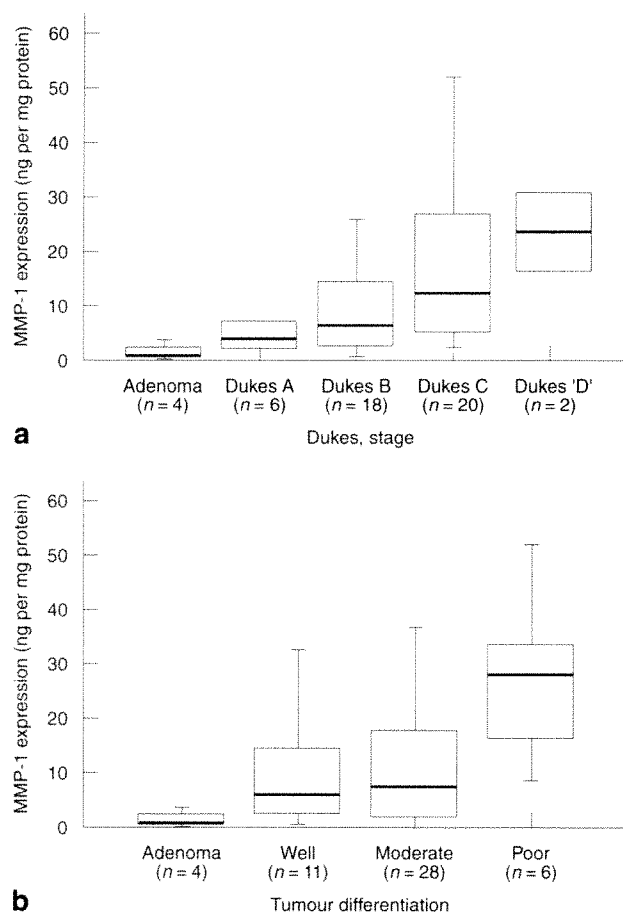


Fig. 3 Boxplots showing differences in matrix metalloproteinase (MMP) 1 levels estimated by enzyme-linked immunosorbent assay according to **a** Dukes stage and **b** tumour differentiation. The horizontal line within the boxplot represents the median value, and interquartile ranges are shown. MMP-1 levels correlated significantly with both Dukes stage and tumour differentiation ($P < 0.05$, Spearman correlation)

Tissue inhibitor of metalloproteinases 1 expression

TIMP-1 levels were significantly greater in tumour than in normal colorectal tissue ($P < 0.05$) (Table 1). TIMP-1 significantly correlated with Dukes stage ($P < 0.05$, Spearman correlation) (Table 2). Tumours that had undergone lymphatic invasion demonstrated significantly greater TIMP-1 levels than non-invasive tumours (90.7 (36.8–212.5) versus 63.9 (25.3–351.2) ng per mg protein; $P < 0.05$). TIMP-1 also significantly correlated with MMP-1 levels ($P < 0.05$, Spearman correlation).

Tissue inhibitor of metalloproteinases 2 expression

TIMP-2 levels were significantly greater in normal colorectal tissue than in tumour tissue ($P < 0.05$) (Table 1). TIMP-2 concentration correlated significantly with lymphatic invasion, invasive tumours demonstrating greater TIMP-2 levels than non-invasive tumours (2.5 (0.9–8.4) versus 1.6 (0–10.4) ng per mg protein; $P < 0.05$).

Total matrix metalloproteinase activity

The total MMP activity or rate of substrate hydrolysis (RSH), as determined by QFSH, was significantly greater in tumour tissue than in corresponding normal colon ($P < 0.05$) (Table 1). The RSH was lower in adenomas than any Dukes stage tumour (Table 2) and was similar to the RSH observed in normal colorectal tissue. The RSH correlated significantly with the tumour depth, with T₃ and T₄ tumours demonstrating a greater RSH than T₁ or T₂.

Discussion

Proteolysis is thought to occur when MMP activity exceeds inhibitor expression. There are advantages and disadvantages to each technique employed in this study; although quantitative, the ELISAs employed measure total MMP

Table 2 Differences in levels of matrix metalloproteinases and tissues inhibitors of metalloproteinases and total matrix metalloproteinase activity with Dukes stage

	MMP-1 (ng mg protein ⁻¹)	MMP-3 (ng mg protein ⁻¹)	TIMP-1 (ng mg protein ⁻¹)	TIMP-2 (ng mg protein ⁻¹)	Total MMP activity (pmol l ⁻¹ min ⁻¹ mg protein ⁻¹)
Adenoma (n=4)	0.8 (0.2–3.6)	1.0 (0.2–18.4)	56.7 (44.2–114.9)	2.8 (1.2–4.8)	4975 (1750–5600)
Dukes stage					
A (n=6)	3.9 (0.1–21.0)	5.2 (2.1–15.6)	66.4 (25.3–68.8)	1.6 (1.0–8.0)	12675 (7150–23800)
B (n=18)	6.1 (0.6–32.3)	7.2 (0.6–43.5)	58.5 (26.4–125.8)	1.5 (0–10.4)	22325 (1750–83600)
C (n=20)	12.1 (0.3–52.1)	5.9 (0.9–69.1)	92.1 (36.8–212.5)	2.2 (0.9–8.4)	13925 (2200–174400)
'D' (n=2)	23.5 (16.3–30.8)	13.1 (7.5–18.8)	141.2 (70.0–212.5)	3.9 (3.1–4.6)	15150 (8500–21800)

Values are median (range). MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases

and TIMP protein levels and do not distinguish between the latent and active forms of MMPs or MMP–TIMP complexes. Zymography does separate latent and active forms of MMPs, but it is still unable to distinguish between free MMPs and MMP–TIMP complexes. The technique of QFSH measures the total amount of 'free' active MMPs and is therefore more likely to be representative of proteolysis *in vivo* than other techniques.

The protein levels of the four MMPs studied were significantly greater in colorectal tumours than in adjacent normal tissue. The interactions of these MMPs with their inhibitors, TIMP-1 and TIMP-2, appear complex: TIMP-1 protein levels were significantly greater in tumour tissue but TIMP-2 levels were significantly greater in the adjacent normal tissue. However, overall total MMP activity was significantly greater in tumour tissue and therefore the balance of MMP and TIMP levels is likely to favour proteolysis. The results of previous studies on MMP and TIMP expression in human colorectal cancer are summarized in Table 3. Despite some conflicting results on the

contribution or expression of MMPs in colorectal cancer progression, the levels of several MMPs, including the four analysed in the present study, have been found to be consistently greater in tumour tissue than in normal tissue or benign adenomas. Increased expression of matrilysin (MMP-7)²⁶, stromelysin 3 (MMP-11)²⁷ and membrane-type MMP-1²⁸ has also been demonstrated in tumour tissue.

Gelatinases are the most extensively studied MMPs and appear to be consistently upregulated in colorectal cancer tissue^{10,12,13,19,22,23}. In the present study both the latent and active forms of MMP-2 and MMP-9 were significantly greater in tumour tissue than in normal colon. Correlating gelatinase expression with the tumour stage demonstrated differences in the active bands for both MMP-2 and MMP-9, the active bands being smaller or absent in colorectal adenomas compared with Dukes staged tumours. However, no convincing differences were observed between Dukes A through to Dukes 'D' tumours. This may be due to the small numbers of Dukes A and 'D' tumours compared with Dukes

Table 3 Summary of previous publications on the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human colorectal cancer

Reference	Year	Methods	No. of patients	MMPs studied	TIMPs studied	Results
Garbett <i>et al.</i> ¹³	1999	Z, E	25	1, 2, 3, 9	1	↑Active MMP-2 and MMP-9, MMP-1, TIMP-1 in tumours
Zeng <i>et al.</i> ¹⁷	1999	IH, Z	34	2, 9		↑Active MMP-2 and MMP-9 with tumorigenesis
Parsons <i>et al.</i> ¹⁹	1998	G	53	2, 9		Latent MMP-2 and MMP-9, and active MMP-2: tumour greater than normal
Karakiulakis <i>et al.</i> ²⁰	1997	Z	36 (primary) 4 (secondary)*	2, 9		Expression of MMP-2 and MMP-9: secondary greater than primary tumours
Ring <i>et al.</i> ²¹	1997	IH	212	2, 9	2	Expression not a predictor of outcome
Liabakk <i>et al.</i> ²²	1996	Z, IS	192	2, 9		MMP-2 and MMP-9 tumour greater than normal; Dukes A and C greater than B
Murray <i>et al.</i> ⁸	1996	IH	64	1		MMP-1 expression associated with poor prognosis
Zeng and Guillem ²³	1996	NB, IS, WB, IH	26	9		MMP-9 protein and mRNA expression – macrophages
Gallegos <i>et al.</i> ²⁴	1995	IH	40	1, 2, 3, 9	1	↑MMP-2 and MMP-9 tumour, no MMP-1, MMP-3 – ECM
Zeng and Guillem ⁷	1995	IS	26	9	1	Distinct expression for both on stromal cells
Zeng <i>et al.</i> ²⁵	1996	NB, IS	56 (primary) 10 (secondary)*		1	Greater in primary tumours with distant metastasis
Zucker <i>et al.</i> ¹⁰	1993	EL		9		MMP-9 greater in tumour than normal
Poulsom <i>et al.</i> ¹²	1992	IS, IH	12	2	2	Both MMP-2, TIMP-2 protein and RNA
Levy <i>et al.</i> ⁹	1991	NB, IH	19 (NB) 70 (IH)	2		mRNA tumour greater than normal, IH correlated with Dukes stage

*Secondary tumours were metastases. Z, zymography; E, enzyme-linked immunoassay; IH, immunohistochemistry; IS, *in situ* hybridization; NB, Northern blotting; WB, Western blotting; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; mRNA, messenger RNA; ECM, extracellular matrix

B and C. One previous study detected significantly greater lysis bands for latent MMP-9 and active MMP-2 in Dukes A and C tumours than in Dukes 'D' following gelatin zymography²². The protein levels of interstitial collagenase (MMP-1) and stromelysin 1 (MMP-3) were also significantly greater in colorectal tumours. For both of these MMPs a positive correlation is emerging between increased MMP levels with increasing Dukes stage and differentiation.

TIMP-1 levels were also higher in tumour tissue than in normal colon and, similar to a previous study, TIMP-1 levels were greater in colorectal cancers with metastases (lymphatic and vascular) than in those without²⁵. Zeng and colleagues proposed that increased TIMP-1 expression was in response to the increased induction or production of MMPs within the tumour stroma by colorectal tumour cells²⁵. TIMP-2 levels within tumour tissue were lower than that observed in normal colon; however, TIMP-2 levels within tumours were greater in those that had undergone lymphatic invasion. Previously TIMP-2 synthesis has been correlated with Dukes classification²⁹ and as a predictor of tumour stage²¹.

Total MMP activity has been determined previously in colorectal cancer in only one other study¹³, and similarly MMP activity was greater in tumour than in normal colorectal tissue. As the levels of the four MMPs studied were significantly greater in tumour tissue, it is reasonable to assume that MMP-1, 2, 3 and 9 are at least partially responsible for hydrolysing the fluorescent substrate. The expression of several other MMPs, including matrilysin²⁶ and stromelysin 3²⁷, have also been demonstrated to be raised in colorectal cancer; these are also likely to be involved in the MMP substrate hydrolysis and may explain discrepancies in results between techniques.

The interactions between MMP and TIMP expression in colorectal cancer progression appears complex as the expression of the studied MMPs and TIMP-1 was upregulated in tumour tissue. This may reflect that the local invasion and remodelling of the ECM, which occurs during tumour progression, is tightly regulated and therefore likely to involve increased levels of both proteinases and their inhibitors¹⁴. From the present study MMP-1 levels appear to be most important in colorectal cancer progression, and follow-up of these patients is required to determine whether high MMP-1 levels are associated with a poor prognosis⁸.

In summary, it is apparent from this and previous studies that the expression of both MMPs and TIMPs is important for successful tumour invasion and metastasis. However, further studies are needed to determine the benefit and use of synthetic proteinase inhibitors in the intervention of colorectal cancer progression *in vivo*.

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Hyaluronic acid-based agents do not affect anastomotic strength in the rat colon, in either the presence or absence of bacterial peritonitis

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Background: Hyaluronic acid (HA) agents reduce postsurgical adhesion formation. The effect of their perioperative administration on early anastomotic healing is unknown. This study investigated the influence of two HA-containing agents on the development of strength in colonic anastomosis during the first postoperative week, both in normal rats and in rats with bacterial peritonitis.

Methods: In 90 male Wistar rats a 1-cm segment was resected from the descending colon and an end-to-end anastomosis was constructed. In 108 rats a bacterial peritonitis was induced using caecal ligation and puncture (CLP). Some 24 h after CLP the abdomen was reopened, the caecum was taken out and, after resection of a 1-cm segment, an anastomosis was made. Animals in both groups were randomized to receive either an HA-carboxymethylcellulose (CMC) bioresorbable membrane, 0.4 per cent HA solution or no treatment. One-third of each group was killed at day 1, 3 and 7 after operation. Cultures were taken from the abdominal cavity for microbiological analysis in half of the animals. Subsequently, both bursting pressure and breaking strength were determined as parameters for anastomotic strength.

Results: No differences in anastomotic bursting pressure or breaking strength were found between the experimental groups and their controls. In addition, there was no significant difference in the number of bacteria cultured from the abdominal cavity between rats treated with HA and controls.

Conclusion: Neither HA-CMC bioresorbable membrane nor 0.4 per cent HA solution interferes with the development of early anastomotic strength in the colon, and can therefore be safely used to prevent intra-abdominal adhesion formation after performing bowel anastomosis.

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Introduction

Postsurgical intra-abdominal adhesion formation may result in severe complications. It is the most common cause of small bowel obstruction in the Western world and is accompanied by marked morbidity and mortality. In addition, intra-abdominal adhesions complicate relaparotomy and are associated with infertility and chronic pelvic pain^{1–4}.

Several agents have been investigated for their efficacy in preventing intra-abdominal adhesions. These include dextran, corticosteroids, phosphatidylcholine, phospholipase inhibitors, non-steroidal anti-inflammatory drugs, heparin and tissue plasminogen activator⁵. However, none of these has been proven to be effective without serious adverse effects. Recent preclinical and clinical studies have

demonstrated that hyaluronic acid (HA)-based agents, such as HA-carboxymethylcellulose (CMC) bioresorbable membrane and HA solution, reduce postsurgical adhesion formation effectively, without apparent side-effects^{6–11}. For example, intra-abdominal adhesion and abscess formation in a rat peritonitis model were reduced using a 0.4 per cent HA solution¹².

HA is a biocompatible, non-toxic, high molecular weight polyanionic polysaccharide, consisting of repeating units of alternating *N*-acetylglucosamine and D-glucuronic acid. It is found in all vertebrate tissues and body fluids¹³. HA instilled in the abdominal cavity is probably absorbed through lacunae in the diaphragmatic surface of the peritoneum, and degraded like endogenous HA, mainly in lymph and blood, but also in the liver¹⁴.

Abdominal surgery frequently includes the construction of a bowel anastomosis. The clinical use of HA-based agents in the perioperative period would be seriously limited if they proved to reduce anastomotic strength, which depends on both the existing and newly deposited extracellular matrix. HA may influence extracellular matrix organization by regulation of both fibroblast collagen production¹⁵ and collagen fibril integrity¹⁶. It therefore seems essential to investigate the possible effects of HA-based agents on anastomotic strength, particularly in the first postoperative week when wound strength is low, even under optimal healing conditions¹⁷. Any adverse effect would be even more serious under conditions of impaired healing, such as appears to be the case during intra-abdominal sepsis¹⁸. In the latter case, adhesion formation is strongly increased¹², emphasizing the need for preventive measures.

The present experiment was performed to investigate the effects of HA-based agents on the development of anastomotic strength during the first postoperative week. For this purpose, colonic anastomoses, constructed in both normal rats and animals with bacterial peritonitis, were treated immediately after operation with either an HA solution or an HA-CMC bioresorbable membrane.

Materials and methods

Design of the study

Male Wistar rats (Harlan Nederland, Zeist, The Netherlands) were allowed to become accustomed to laboratory conditions for 1 week before experimental use. Animals were housed at 21°C with a day-night cycle of 12 h. They had free access to water and standard rodent chow (Hope Farms, Woerden, The Netherlands). The study protocol was approved by the animal ethics review committee of the Faculty of Medicine, University of Nijmegen.

Experiment 1: normal rats

Ninety rats, weighing between 250 and 300 g, were anaesthetized with a fluothane (AstraZeneca, Wilmslow, UK)-nitrous oxide-oxygen mixture. The abdomen was shaved, disinfected with 70 per cent alcohol and opened via a 3-cm midline incision. The descending colon was mobilized and a 1-cm segment was resected 3 cm proximal to the peritoneal reflection. Subsequently, an inverted single-layer end-to-end anastomosis was constructed with eight interrupted sutures of 8/0 monofilament material (Ethicon, Norderstedt, Germany).

Animals were randomized into three groups ($n = 30$ each). Rats in the first group remained untreated and served as

controls. In the second group 1 × 3-cm HA-CMC bioresorbable membrane (Seprafilm; Genzyme, Cambridge, Massachusetts, USA) was wrapped around the anastomosis and 3 × 4 cm of the same material was left under the midline incision. In the third group the abdominal cavity was coated with 3 ml 0.4 per cent HA solution (Sepracoat; Genzyme) before any manipulation of the viscera, and after completing the anastomosis a further 5 ml HA solution was instilled in order to fill the whole abdominal cavity. The abdomen was closed in two layers using a 3/0 polyglactin suture for the fascia and staples for the skin. After operation rats were resuscitated with 10 ml saline subcutaneously. One-third of the animals in each group were killed, by carbon dioxide asphyxiation, at days 1, 3 and 7 after operation.

Seprafilm and Sepracoat were kindly donated by Genzyme.

Experiment 2: rats with peritonitis

In 108 rats, weighing between 250 and 320 g, a bacterial peritonitis was induced using a caecal ligation and puncture (CLP) model, with minor modifications¹⁹. Rats were fasted for 12 h, anaesthetized, shaved and disinfected as described above. Via a 3-cm midline laparotomy, the caecum was dissected without damaging the vascularization and was filled backwards with faeces. Thereafter, the caecum was ligated immediately distal to the ileocaecal valve, with a 3/0 polyglactin suture, and punctured once with a 19-G needle at the antimesenteric site. The abdominal wall was closed in two layers using a 3/0 polyglactin suture. Immediately after operation, rats received a single dose of gentamicin 6 mg/kg body-weight intramuscularly and buprenorphine 0.1 mg/kg body-weight subcutaneously. All animals were resuscitated with 10 ml saline subcutaneously. After 24 h the abdomen was reopened. The ligated caecum was resected, and a colonic end-to-end anastomosis constructed as described above. Again, animals were randomized into three subgroups ($n = 36$): a control group, a group treated with HA-CMC bioresorbable membrane, and a group treated with 0.4 per cent HA solution, as described above. One-third of the animals in each group were killed at days 1, 3 and 7 by carbon dioxide asphyxiation.

Analysis

The abdominal wall was disinfected with 70 per cent alcohol and reopened. From half of the animals in each group samples of peritoneal fluid were collected in a BBL Port-A-Cul envelope (Becton Dickinson, Cockeysville, Maryland, USA) for microbiological analysis. The anastomoses were carefully resected, without dissecting adhesions, for the measurement of bursting pressure and breaking strength.

Bursting pressure and breaking strength

Faecal material was removed from the colonic segment, which was then attached to an infusion pump and a device that recorded internal pressure. Subsequently, pressure was increased by pumping an aqueous solution of methylene blue into the segment, which was kept under water. Loss of pressure, indicating leakage, was recorded immediately and the site of perforation was indicated by the loss of methylene blue.

After determination of the bursting strength, the breaking strength was measured in the same segment. Previous experiments have demonstrated that measurement of the bursting pressure does not interfere with measurement of breaking strength of the same anastomosis²⁰. The segment was clamped in a device that exerts a continuously increasing force in a longitudinal direction. The peak force necessary to induce a disruption was noted as the breaking strength.

Bacterial cultures

Samples of peritoneal fluid and abscesses were cultured semiquantitatively under aerobic and anaerobic conditions. Colombia III agar with 5 per cent sheep blood (Becton Dickinson, Etten-Leur, The Netherlands), Levine eosin methylene blue agar (Oxoid, Haarlem, The Netherlands) and fastidious anaerobic agar (Tapley, Bury, UK) with and without kanamycin were used. After 24 and 48 h of incubation at 37°C, bacteria were identified according to standard procedures.

Statistical analysis

The statistical tests used are described within the text. $P < 0.05$ was considered significant. All tests were two tailed.

Results

Experiment 1: normal rats

One day after operation rats lost an average 5 per cent of their body-weight. On the third day the loss in body-weight was 2 per cent. At day 7 a 5 per cent increase in body-weight was seen, compared with the weight before operation. No significant differences in body-weight were observed between rats treated with 0.4 per cent HA solution or HA-CMC membrane and control rats.

During the experiment one of the 30 rats treated with HA-CMC membrane died. Autopsy showed dehiscence of the anastomosis encapsulated in an abscess. None of the

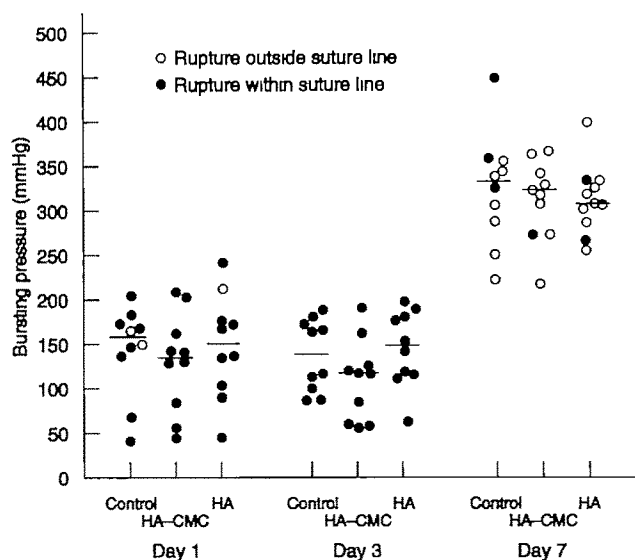


Fig. 1 Anastomotic bursting pressures in normal rats treated with hyaluronic acid-carboxymethylcellulose membrane (HA-CMC), 0.4 per cent hyaluronic acid solution (HA) and controls. Horizontal bars represent median values

control rats or rats treated with HA solution died prematurely.

Bursting pressure and breaking strength

In all groups the bursting pressures (Fig. 1) and breaking strengths (Fig. 2) of the anastomotic segment were significantly higher at day 7 than at day 1 or 3 ($P < 0.001$, Mann-Whitney U test). At days 1 and 3 the bursting sites were almost invariably within the anastomoses. There was no significant difference in bursting pressure between groups treated with HA-CMC or HA solution and the controls. Similar results were found at day 7, when the bursting site was mostly outside the suture line. When analysing the breaking strength, disruption invariably occurred within the anastomotic area. Treatment with either HA-CMC bioresorbable membrane or 0.4 per cent HA solution did not significantly affect the breaking strength at any of the time points analysed.

Microbiological analysis

One day after operation bacterial growth of 10^4 to 10^5 colony-forming units (c.f.u.) per ml was found in the peritoneal fluid samples from three of five animals in the HA-CMC group, two of five in the HA solution group, and two of five in the control group. Bacteria present were *Escherichia coli* and *Lactobacillus* species. At day 3 a mixed

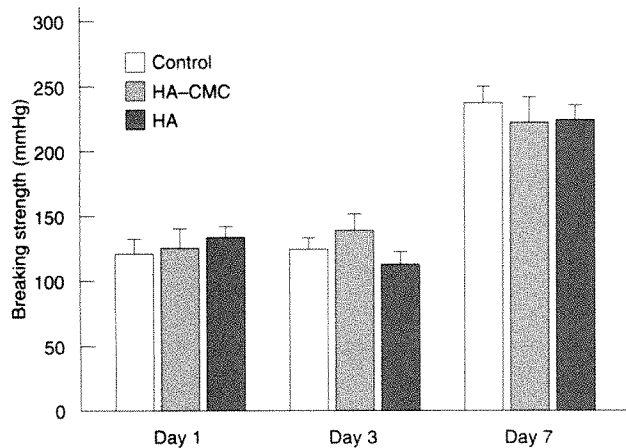


Fig. 2 Anastomotic breaking strength in normal rats treated with hyaluronic acid-carboxymethylcellulose membrane (HA-CMC), 0.4 per cent hyaluronic acid solution (HA) and controls. Values are mean(s.e.m.)

faecal flora was cultured in a concentration of 10^4 c.f.u. per ml in two of five samples collected from control rats. All samples from the HA-CMC group and two of five from the HA solution group revealed polymicrobial growth in a concentration of 10^4 to 10^5 c.f.u. per ml. Bacteria isolated were *E. coli*, enterococci, *Bacteroides* species and staphylococci. At day 7 microbial growth was found in all samples in concentrations of 10^5 to 10^8 c.f.u. per ml. Bacteria most abundantly present were enterococci, *E. coli*, *Proteus* species and staphylococci. At no time point was there any significant difference between groups. One week after operation only one rat in each group had developed a minor abscess (less than 3 mm).

Experiment 2: rats with peritonitis

One day after resecting and anastomosing the colon, rats had lost an average 8 per cent body-weight. At day 3 average weight lost was 5 per cent, and at day 7 average weight had increased 1.5 per cent over the weight recorded immediately before operation. There were no significant differences in weight between groups treated with 0.4 per cent HA solution or HA-CMC membrane and the control groups.

One day after CLP all rats had developed peritonitis with fibrous exudate and pus in the abdomen. They exhibited symptoms of sepsis including apathetic behaviour, ocular exudes, piloerection and diarrhoea. These symptoms resolved within 2 days after removing the ligated and perforated caecum.

During the experiment 18 (17 per cent) of 108 rats died prematurely. Two rats died immediately after anaesthesia on the day of CLP. Fourteen rats died on the first day after

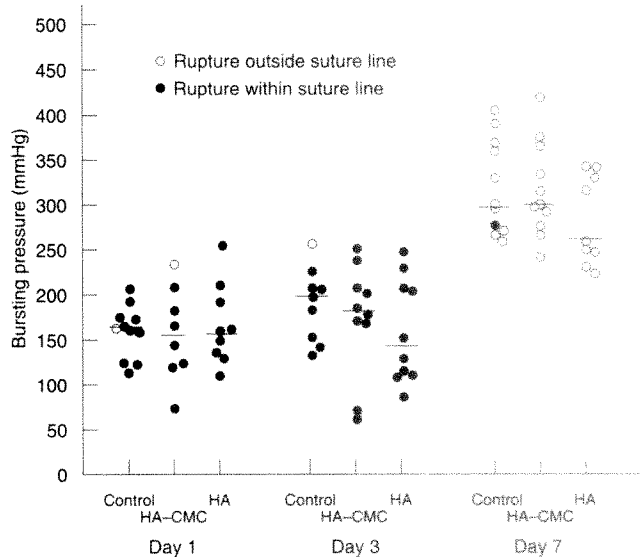


Fig. 3 Anastomotic bursting pressures in rats with peritonitis treated with hyaluronic acid-carboxymethylcellulose membrane (HA-CMC), 0.4 per cent hyaluronic acid solution (HA) and controls. Horizontal bars represent median values

performing the colonic anastomosis. The remaining two died on days 2 and 3. Six rats that prematurely died were treated with HA solution, six were treated with HA-CMC membrane and four were controls. There was no significant difference in mortality rate between the groups. In all rats septicaemia caused by CLP was considered the cause of death. In all of them, large volumes of peritoneal fluid and dilated bowels were found at autopsy.

Bursting pressure and breaking strength

As in experiment 1, in all groups the bursting pressure (Fig. 3) and breaking strength (Fig. 4) were significantly higher at day 7 than at days 1 and 3 ($P < 0.001$, Mann-Whitney *U* test). The bursting site was mostly within the suture line at days 1 and 3, and outside the suture line at day 7. At neither time point did treatment with HA-CMC bioresorbable membrane or 0.4 per cent HA solution significantly affect the bursting pressure. Again, when analysing the breaking strength, disruption invariably occurred within the anastomotic area, while no significant differences were observed between experimental and control groups.

Microbiological analysis

One day after anastomosing the colon, large volumes of peritoneal fluid were present in the abdominal cavity.

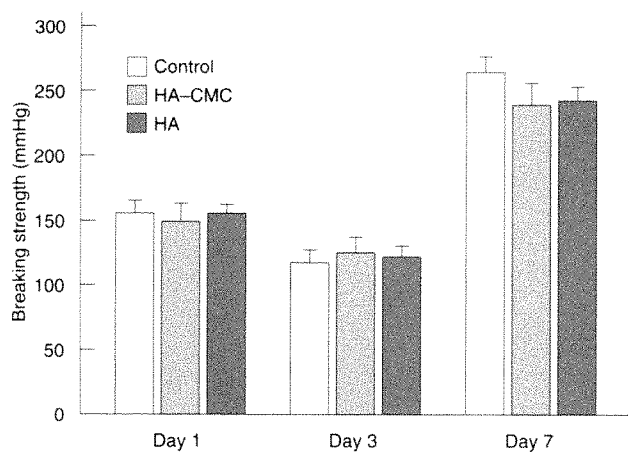


Fig. 4 Anastomotic breaking strength in rats with peritonitis treated with hyaluronic acid–carboxymethylcellulose membrane (HA-CMC), 0.4 per cent hyaluronic acid solution (HA) and controls. Values are mean(s.e.m.)

Bacterial analysis of the fluid revealed a polymicrobial growth in concentrations of 10^4 to 10^8 c.f.u. per ml. Bacteria present were enterococci, *E. coli*, staphylococci and *Bacteroides* species. Three days after anastomosis bacteria were cultured from all samples. The same bacteria as on day 1 were found in concentrations of 10^4 to 10^6 c.f.u. per ml. At day 7 bacteria were present in all rats treated with HA solution, in four of six HA-CMC-treated rats, and in all control rats in concentrations of 10^4 to 10^6 c.f.u. per ml. There was no significant difference between groups. One week after anastomosis seven of ten control rats and nine of 11 rats treated with HA-CMC had developed an intra-abdominal abscess. In contrast, only three of nine rats treated with 0.4 per cent HA solution had an intra-abdominal abscess. These differences remained statistically non-significant (Fisher's exact test).

Discussion

This study demonstrated that the use of HA-based agents does not interfere with the development of colonic anastomotic strength, regardless of the presence or absence of bacterial peritonitis.

Efforts to control postsurgical adhesion formation are especially important following procedures that cause extensive surgical trauma, which frequently include the construction of bowel anastomosis²¹. Results from the present study suggest that HA-containing agents can be used safely, with respect to early anastomotic repair, to prevent adhesions. Previous studies have reported similar results, at least under non-infectious conditions^{22,23}. In these studies anastomotic strength was measured 7 or

14 days after operation, when the bursting pressure, which was the parameter used, does not reflect wound strength because the bursting site (which was unreported) is almost invariably outside the suture line at this time¹⁷. Clinically, colonic anastomoses are at risk for leakage mostly within the first week after operation. Animal studies have shown that anastomotic strength is relatively low in this period¹⁷. This is also obvious from the present data: wound strength at days 1 and 3 was significantly lower than that on day 7. Thus, any reduction in strength in the early postoperative days may be expected to be more threatening to anastomotic integrity than loss of strength in the second week after operation; hence this study was limited to the first 7 days after surgery. Two parameters were utilized to analyse anastomotic strength. The bursting pressure is a measure of resistance to increasing intraluminal pressure, while the breaking strength is a measure for the ability to withstand longitudinal forces. The former is affected by minor gaps in the intestinal wall, which will leave the latter unchanged. In both groups similar results were obtained for both parameters.

The role of fibrinous adhesions in early anastomotic strength is not fully understood. It is possible that postoperative adhesions, formed around the anastomosis, increase early anastomotic strength. However, when 'artificial' abdominal adhesions were created using fibrin to seal the colonic anastomosis, no increase in wound strength was found^{24–26}. Van der Ham *et al.*²⁷ even demonstrated a decrease in colonic anastomotic strength on day 4 using fibrin sealant. It seems that fibrinous adhesions do not have a beneficial role in the development of early anastomotic strength of the colon and thus it is not entirely unexpected that adhesion prevention by HA agents leaves anastomotic strength intact.

Anastomoses constructed in an infected environment are generally considered to exhibit reduced strength¹⁸. This reduction is presumed to be caused by a decreased collagen content of the wound^{18,28}. There is also evidence of a negative effect of fibrinous adhesions on the anastomotic healing process in a contaminated environment²⁶, rather than a positive effect, which is commonly believed by surgeons. The role of perianastomotic fibrin has been outlined by Houston *et al.*²⁹ who showed that, if fibrin is degraded by tissue plasminogen activator (tPA), the deleterious effect of infection on colonic anastomotic strength is reduced. These surprising data are probably explained by the capacity of fibrin to sequester and wall off bacteria³⁰ and impair host defence mechanisms in the peritoneal cavity³¹, leading to ongoing focal infection and abscess formation. By degrading fibrin, bacteria spread out throughout the abdominal cavity and may become accessible to neutrophils and macrophages. The adverse

effect of bacterial load on anastomoses is supported by the finding that the addition of antibiotics to the fibrin sealant prevents its negative effect on colonic anastomotic healing³².

In contrast to tPA, HA did not have any influence on early colonic anastomotic strength in an infected environment, despite its similarity in adhesion and abscess-reducing capacity^{12,33}. The mechanism of action of HA does not seem to involve the peritoneal fibrinolytic system. A direct antibacterial effect of HA may also be ruled out as there was no difference in the presence and number of bacteria in the abdominal cavity between HA-treated rats and controls. Other mechanisms may be involved, as previously described by the authors' group¹².

Data on the effect of HA on anastomotic healing in an infectious environment may not be extrapolated to other 'compromised' anastomoses, such as those with marginalized blood flow or tenuous suture lines. Under these circumstances neovascularization, encouraged by formation of adhesions, may be important to overcome degrees of ischaemia, and then this process is impaired by HA. As such anastomoses continue to be made in humans, the effect of HA should be assessed in models of ischaemic anastomosis.

In conclusion, this study has demonstrated that the use of HA-CMC bioresorbable membrane or 0.4 per cent HA solution does not affect early anastomotic strength of the colon in the presence and absence of bacterial peritonitis. It is therefore suggested that both agents can be safely used in the perioperative period in order to prevent intra-abdominal adhesion formation in the presence of an anastomosis.

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Diagnosis and treatment of portal vein thrombosis following splenectomy

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Background: Portal vein thrombosis is a rare but potentially fatal complication of splenectomy. The aim of this study was to assess the incidence, risk factors, treatment and outcome of portal vein thrombosis after splenectomy in a large series of patients.

Methods: All patients who had undergone a splenectomy in the University Hospital, Rotterdam, between 1984 and 1997 were reviewed retrospectively. Splenectomy that was followed by symptomatic portal vein thrombosis was selected for analysis. Risk factors for portal vein thrombosis were sought.

Results: Of 563 splenectomies, nine (2 per cent) were complicated by symptomatic portal vein thrombosis. All these patients had either fever or abdominal pain. Two of 16 patients with a myeloproliferative disorder developed portal vein thrombosis after splenectomy ($P=0.03$), and four of 49 patients with haemolytic anaemia ($P=0.005$). Treatment within 10 days after splenectomy was successful in all patients, while delayed treatment was ineffective.

Conclusion: Portal vein thrombosis should be suspected in a patient with fever or abdominal pain after splenectomy. Patients with a myeloproliferative disorder or haemolytic anaemia are at higher risk; they might benefit from early detection and could have routine Doppler ultrasonography after splenectomy.

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Introduction

Portal vein thrombosis is a rare but potentially fatal complication of splenectomy¹. The first case was described by Beeckman Delatour in 1895². Since then, sporadic reports of portal vein thrombosis have appeared^{3–9}. The incidence of portal vein thrombosis appears low, but is probably underestimated because symptoms, such as abdominal pain and fever, are non-specific and portal vein thrombosis can easily develop without any symptoms¹⁰.

Identification of patients with portal vein thrombosis is crucial to allow early treatment and prevent potentially fatal complications such as bowel infarction or later portal hypertension¹. The aim of this study was to assess the incidence of symptomatic portal vein thrombosis after splenectomy in a large series of patients, to document disorders predisposing to portal vein thrombosis and to assess the treatment and its outcome.

Patients and methods

A computerized record search was conducted to identify all patients who had had a splenectomy at the Erasmus Medical

Centre, Rotterdam, between January 1984 and December 1997. The indication for splenectomy was registered for all patients. Patients who were diagnosed with portal vein thrombosis after operation or at follow-up were selected for further analysis. Clinical characteristics, thromboprophylaxis, operative findings, postoperative course and follow-up were documented for these patients. The indications for splenectomy in the groups with and without portal vein thrombosis were compared with Fisher's exact test; $P < 0.05$ was considered significant.

Results

During the study interval, 563 patients had a splenectomy (Table 1). Splenectomy was necessary during resection of a malignant tumour of an abdominal organ in 166 patients. The remainder included 122 operations for trauma and 104 splenectomies for inadvertent injury.

Nine patients (2 per cent), five female and four male patients, developed symptomatic portal vein thrombosis after splenectomy. Their mean age was 32 (range 6–68) years. In eight of these nine patients, preoperative ultrasonography was performed and had shown no sign of

Table 1 Indications for splenectomy

	No PVT	PVT	<i>P</i>
Haematological malignancy			
Myeloproliferative disorder	16	2	0.03
Lymphoproliferative disorder	24	0	n.s.
Malignant histiocytosis	1	0	n.s.
Haemolytic anaemia	45	4	0.005
Idiopathic thrombocytopenia	68	0	n.s.
Inadvertent splenic injury during abdominal surgery	104	0	n.s.
Traumatic ruptured spleen	122	0	n.s.
Oncological resection	166	1	n.s.
Splenic cyst	0	1	n.s.
Portal hypertension	0	1	n.s.
Other	9	0	n.s.

PVT, portal vein thrombosis; n.s., not significant. *Fisher's exact test

portal vein thrombosis. The associated diseases were haemolytic anaemia ($n = 4$), idiopathic splenomegaly (later diagnosed as chronic myeloid leukaemia; $n = 1$), polycythaemia rubra vera ($n = 1$), splenic cyst ($n = 1$), portal hypertension in hepatic nodular regenerative hyperplasia with splenomegaly ($n = 1$) and carcinoid tumour of the stomach ($n = 1$). Of the patients with haemolytic anaemia, three had a hereditary form and one had autoimmune haemolytic anaemia.

In the group with portal vein thrombosis the indications for splenectomy were thrombocytopenia or anaemia requiring blood transfusion, persistent abdominal pain due to splenomegaly and *en bloc* resection of a carcinoid tumour of the stomach.

The incidence of portal vein thrombosis was two of 16 for patients with a myeloproliferative disorder, four (8 per cent) of 49 in patients with haemolytic anaemia and one (1 per cent) of 167 in patients who had splenectomy as part of a radical oncological procedure. No patient with a lymphoproliferative disorder, iatrogenic splenectomy, traumatic lesion or idiopathic thrombocytopenia had portal vein thrombosis. Statistical analysis with Fisher's exact test showed that both haemolytic anaemia ($P = 0.005$) and myeloproliferative disorder ($P = 0.03$) were significant risk factors for developing portal vein thrombosis after splenectomy (Table 1).

Preoperative prophylactic anticoagulant therapy with low molecular weight subcutaneous heparin was administered in seven of the nine patients who developed portal vein thrombosis. One patient with von Willebrand disease did not have prophylaxis but received factor VIII-von Willebrand factor instead. The other patient did not have thromboprophylaxis because of his young age (6 years).

Of the nine patients who developed portal vein thrombosis, three had marked splenomegaly of 1211, 1735 and

2730 g. The median splenic weight in patients who developed portal vein thrombosis was 660 (mean 975; range 240–2730) g. Four patients had postoperative thrombocytosis with a platelet count exceeding $1200 \times 10^9/\text{litre}$. The median platelet count at the time of portal vein thrombosis diagnosis was 827 (range 375–1447) $\times 10^9/\text{litre}$, while the median postoperative maximum platelet count was 1020 (range 609–1490) $\times 10^9/\text{litre}$.

Symptoms in the nine patients with portal vein thrombosis included abdominal pain in six and fever (rectal body temperature greater than 38°C) in all nine. Abdominal pain was located mainly in the left upper quadrant, but in some patients was diffuse. In three patients there were coexisting abdominal complications including a bile collection, an infected haematoma and a subphrenic abscess. In these patients the fever and abdominal pain could not be attributed to the portal vein thrombosis alone.

Portal vein thrombosis was not suspected initially in any patient. When abdominal pain, fever or leucocytosis developed, ultrasonography of the abdomen was performed to look for an abscess. In seven patients, portal vein thrombosis was diagnosed with colour Doppler ultrasonography. In one patient, portal vein thrombosis was discovered at computed tomography (CT), which was performed to assess drainage of a subphrenic abscess. In these eight patients the median interval between splenectomy and diagnosis of portal vein thrombosis was 12 (range 6–99) days.

In the remaining patient, the interval between splenectomy and diagnosis of portal vein thrombosis was 9 years. On case note review this patient had a fever of 38°C on the sixth and seventh postoperative day. Nine years after splenectomy she presented with hepatomegaly and haematemeses. Ultrasonography showed portal vein thrombosis with cavernous transformation and collateral flow.

The extension of the thrombus varied. In at least six patients the thrombus extended into the splenic vein (in three patients the aspect of the splenic vein was not described), and in five of these thrombus was also found in the superior mesenteric vein.

Management of portal vein thrombosis

After diagnosis of portal vein thrombosis, prompt therapy was initiated in eight patients. Six were treated with intravenous heparin combined with warfarin. Two patients were also treated with alteplase (human recombinant tissue plasminogen activator; tPA) directly into the portal vein thrombus through a transhepatic catheter, placed percutaneously. One patient received systemic streptokinase. Another patient was treated with warfarin alone. In one patient prophylactic antithrombotic therapy with daily

subcutaneous injections of 7500 units nadroparin was continued as monotherapy for 1 month after the portal vein thrombosis was diagnosed. No treatment was given to the patient in whom the portal vein thrombosis was discovered 9 years after splenectomy. Only four patients had successful portal vein recanalization: two after routine anticoagulation, one after nadroparin and one after tPA.

In all three patients with portal vein thrombosis who were treated within 10 days after splenectomy, the thrombus in the portal vein resolved on duplex ultrasonography. In the patient who received daily administration of nadroparin, the flow in the portal vein was restored as well. At ultrasonographic follow-up (range 1.5–3 years) all portal veins remained patent in the patients who responded to treatment. In three patients studied by duplex scanning in whom the interval between splenectomy and initiation of therapy was 10 days or longer, no effect on the thrombus was seen and extensive collateral flow developed. In two patients, one with gastric carcinoid, who was treated after 16 days, and the patient who did not receive treatment, no further imaging of the portal vein thrombosis was conducted.

Complications

Two patients developed early complications: one, treated with heparin, alteplase and warfarin, developed subcutaneous bleeding in a laparotomy wound that was ligated under local anaesthesia. The other, who was treated with heparin and warfarin, had recurrent nose bleeds for several days after operation.

Two of the three patients with portal vein thrombosis who failed to respond or did not receive any treatment developed oesophageal varices. One presented with oesophageal variceal bleeding 9 years after splenectomy, and oesophageal varices were found incidentally in the other patient. None of the patients in this study developed the fatal complication of bowel necrosis as a result of portal vein thrombosis.

Discussion

Portal vein thrombosis is a dreaded complication of splenectomy. Hypercoagulability after splenectomy and stasis of blood in the stump of the splenic vein appear to predispose to portal vein thrombosis^{1,10,11}.

Splenectomy is followed by increased viscosity due to high platelet and leucocyte counts as a result of absent splenic breakdown¹². In the present study, postoperative thrombocytosis occurred in all nine patients with portal vein thrombosis, while four had platelet counts exceeding $1200 \times 10^9/\text{litre}$. Another sequel of splenectomy is in-

creased rigidity of erythrocytes possibly caused by the accumulation of nuclear remnants (e.g. Howell-Jolly bodies); the greater rigidity contributes to a higher plasma viscosity¹³.

Stasis of blood in the stump of the splenic vein may be a mechanical risk factor for thrombosis of the portal vein. In patients with a large spleen, the stump of the splenic vein that remains after ligation forms a cul de sac^{1,4,14}. Turbulence in this cul de sac can result in thrombosis, which can spread into the portal and superior mesenteric veins. There is a correlation between the size of the spleen and the diameter of the splenic vein; therefore, splenomegaly possibly increases the risk of portal vein thrombosis. The mean splenic weight in patients with portal vein thrombosis in the present study was 975 g, six times normal splenic weight. Some authors believe that a long splenic vein stump increases the risk for portal thrombosis as well. They recommend ligation of the splenic vein as close as possible to the junction with the superior mesenteric vein or the inferior mesenteric vein.^{1,15} The disadvantages of this technique are bleeding from the splenic vein and its pancreatic tributaries and pancreatic injury. Furthermore, evidence is lacking that this technique prevents portal vein thrombosis.

The incidence of symptomatic portal vein thrombosis after splenectomy varies from 0.2 to 0.9 per cent in retrospective studies^{16,17}. In these studies, portal vein thrombosis has frequently been described with concomitant extensive visceral gangrene. Charleux *et al.*^{17,18} reported two patients with portal vein thrombosis, one with a fatal outcome, among 1036 patients. Benchimol *et al.*¹⁹ noted one portal vein thrombosis with fatal complications among 109 patients (0.9 per cent). Rattner *et al.*¹ identified seven cases of portal vein thrombosis among 1000 patients (0.7 per cent), with two deaths, while Broe *et al.*⁴ identified five patients with portal vein thrombosis among 28 patients operated on for myeloid metaplasia, all of whom had fatal complications. In contrast to other studies^{1,4,17–19}, visceral gangrene was not encountered in the present study. In other studies that reported visceral gangrene, patients did not receive preoperative thrombus prophylaxis. Possibly, this played a role in preventing visceral gangrene.

The incidence of asymptomatic portal vein thrombosis seems to be significantly higher than that of symptomatic thrombosis. In a prospective study of 183 patients studied by ultrasonography and CT, Petit *et al.*²⁰ found 13 cases (10.9 per cent). Similar results were found by Chaffanjon *et al.*¹⁰ in their study of 60 patients who had splenectomy for haematological disease, three (5 per cent) developed asymptomatic portal vein thrombosis. Asymptomatic portal vein thrombosis was not recorded in the present study; routine ultrasonography was not performed. At a mean

follow-up of 6 years, complications of asymptomatic portal vein thrombosis were not identified in patients in the present study. It remains to be established whether asymptomatic portal vein thrombosis is associated with long-term sequelae.

In this study, both myeloproliferative disorders and haemolytic anaemia predisposed to portal vein thrombosis after splenectomy. Myeloproliferative disorders are recognized as a risk factor for portal vein thrombosis^{4,21}. Myeloproliferative disorders are associated with splenomegaly and thrombocytosis, and it is unclear whether the increased risk for developing portal vein thrombosis is associated with the disease process and thrombocythaemia or with the splenectomy.

In this study haemolytic anaemia was a significant risk factor as well. Occasional reports of patients with haemolytic anaemia who developed portal vein thrombosis after splenectomy exist, but none with statistical analysis^{1,6,22}. As haemolytic anaemia is not necessarily associated with splenomegaly and thrombocythaemia, this disease could be an independent risk factor.

Colour Doppler imaging has a specificity of 99 per cent and a sensitivity of 93 per cent for detecting portal vein thrombosis. Contrast-enhanced CT is highly specific (99 per cent) but slightly less sensitive (90 per cent)²³. CT may be more accurate in the first 7 days after operation when ultrasonography is often restricted by bowel distension¹⁰. The role of routine ultrasonography in patients with risk factors for portal vein thrombosis (myeloproliferative disorders, haemolytic anaemia, marked splenomegaly and thrombocytosis) is not established. Chaffanjon *et al.*¹⁰ performed a prospective study of 60 patients and suggested that those with risk factors for portal vein thrombosis should have routine ultrasonographic monitoring after operation. This could be done about 5 days after splenectomy when the postoperative ileus has settled, using ultrasonography.

Prompt initiation of therapy for portal vein thrombosis seems to be an important determinant for success. None of the treatments in the present patients was universally effective. The role of prophylactic heparin remains uncertain; seven of nine patients who developed portal vein thrombosis received prophylaxis. In the patient who received prophylactic nadroparin 7500 units subcutaneously, continuation of therapy for 1 month was followed by complete resolution of the thrombus. It is possible that increasing the dosage of prophylactic heparin might be beneficial.

In conclusion, portal vein thrombosis should be suspected in patients with either fever or abdominal pain after splenectomy. Myeloproliferative disease and haemolytic anaemia are both significant risk factors. Early treatment is more likely to restore normal flow in the portal vein and to

prevent portal hypertension. Routine Doppler ultrasonography after splenectomy might enable early diagnosis and effective treatment.

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Estimation of lymph node metastasis by size in patients with intrathoracic oesophageal cancer

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Background: The preoperative evaluation of lymphatic metastasis in patients with oesophageal cancer is of vital importance in determining a therapeutic strategy. The aim of this study was to establish criteria for the preoperative diagnosis of lymph node metastases based on the size and shape of nodes.

Methods: Some 123 patients with intrathoracic oesophageal cancer were studied and 6822 nodes were obtained by extended lymphadenectomy. The nodes were classified anatomically and their size was measured by the operating surgeon during or immediately after operation. All were examined histologically and criteria for the diagnosis of metastasis were evaluated.

Results: The size of the lymph nodes varied by anatomical site. Nodes were smallest in the neck and largest at the tracheal bifurcation. The cut-off value for the diagnosis of metastasis was 5 mm in the neck, 6 mm in the abdomen and 8 mm in the mediastinum, except for tracheal nodes. Lymph nodes 10 mm or larger tended to become spherical when involved by metastasis.

Conclusion: The incidence of metastasis in each lymph node can be estimated by its size. Discounting nodes less than 10 mm can lead to an underestimation of the stage of oesophageal cancer during preoperative evaluation.

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Introduction

Extended lymphadenectomy has revealed that intrathoracic oesophageal cancer tends to metastasize to the cervical, mediastinal and abdominal nodes at an early stage of the disease^{1–3}. Preoperative evaluation of lymphatic metastasis in patients with intrathoracic oesophageal cancer may be helpful in predicting prognosis and determining the optimal therapeutic strategy^{4–7}. Preoperative staging is commonly performed by computed tomography (CT) or endoscopic ultrasonography. Nodal involvement is often diagnosed by the size and shape of the nodes, but the diagnosis is imprecise. The aim of this study was to establish the criteria for estimating the presence of lymph node metastasis, based on the relationship between nodal metastasis and the diameter and/or shape of the nodes, using tissue obtained from patients with oesophageal cancer who underwent extended lymphadenectomy.

Patients and methods

One hundred and twenty-three patients with squamous cell carcinoma of the intrathoracic oesophagus who underwent

oesophagectomy with three-field (neck, mediastinum and abdomen) lymph node dissection between 1986 and 1994 were entered into the study. Patients with fixed cervical nodes or multiorgan involvement were excluded because lymph node dissection is not performed in these patients. Moreover, patients who had preoperative chemotherapy or a medical condition that might involve the cervical, mediastinal or abdominal nodes, such as active cardiovascular or malignant disease, were also excluded. There were 91 men and 32 women, with a mean age at operation of 63 (range 43–80) years. The location of the oesophageal cancer was the upper thorax in ten patients, the middle thorax in 70 and the lower thorax in 43.

The mediastinal lymph nodes were dissected first through a right thoracotomy. The abdominal nodes were dissected through an upper midline incision, and finally cervical nodes as cranial as the caudal border of the omohyoid muscle were dissected on both sides through a collar incision in the neck. According to guidelines for the clinical and pathologic study on carcinoma of the oesophagus from the Japanese Society for Esophageal Disease⁸, each nodal site was classified into one of six anatomical groups (*Table 1*). The nodes along the bilateral recurrent

laryngeal nerves were classified as the recurrent laryngeal nerve nodes⁹, distinct from the guidelines, because these nodes were clinically important and located away from the other paratracheal or paraoesophageal nodes. The recurrent laryngeal nerve nodes were dissected to the level of the caudal border of the thyroid gland by means of a thoracic approach. These were defined as the recurrent laryngeal nerve nodes, although they included some of the cervical nodes.

During or immediately after operation, the dissected nodes were classified into each nodal site by the operating surgeon. Adipose and connective tissues were removed from these lymph nodes, and the longest and shortest diameter of each node was measured before fixation with 20

per cent formalin. Histological diagnosis of the presence or absence of metastatic disease in each node was then made on a section with the maximum surface area stained with haematoxylin and eosin by pathologists who were not informed about clinical stage or site of the nodes.

The longest diameter was used as an index of the size of the node, and the ratio of the shortest:longest diameter (S:L ratio) was calculated and served as an index of the shape of the node. To calculate the optimal reference values for diagnosing lymph node metastasis based on size, receiver–operator characteristic (ROC) analysis^{10,11} was performed. Reference values per millimetre length of node in each group were obtained, and the sensitivity and specificity were calculated. Sensitivity (percentage) was plotted on the vertical axis, whereas 100–specificity (percentage) was plotted on the horizontal axis. The nearest point from each ROC curve to the point corresponding to 100 per cent sensitivity and 0 per cent (100–specificity) is the one that offers the highest specificity and sensitivity simultaneously in each nodal group. The size of the node at that nearest point was regarded as the cut-off value for the diagnosis of metastasis. ROC analysis was also performed with regard to the shape of the node, and the criterion point for the diagnosis of metastasis was estimated in a similar manner.

Statistical differences in the sizes of metastatic and non-metastatic nodes in each node group were analysed with the Welch *t* test. Any correlation between the presence of metastasis and shape was determined with the χ^2 test.

Results

Lymph node metastases were detected in 89 (72 per cent) of 123 patients. The total number of dissected lymph nodes was 6822, consisting of 520 from the neck, 3824 from the mediastinum and 2478 from the abdomen. Involved nodes

Table 1 Grouping of each lymph node site

Group	Site of lymph node
A	Superficial cervical nodes
	Cervical paraoesophageal nodes
	Deep cervical nodes
	Supraclavicular nodes
B	Bilateral recurrent laryngeal nerve nodes
	Infra-aortic arch nodes
C	Tracheal bifurcation nodes
	Paratracheal nodes
	Pulmonary hilar nodes
D	Upper thoracic paraoesophageal nodes
	Middle thoracic paraoesophageal nodes
	Lower thoracic paraoesophageal nodes
	Posterior mediastinal nodes
	Diaphragmatic nodes
E	Right cardiac nodes
	Left cardiac nodes
F	Lesser curvature nodes
	Left gastric artery nodes
	Common hepatic artery nodes
	Coeliac axis nodes

Table 2 Size of lymph nodes and cut-off value in each group

Group	Long axis (mm)*		Short axis (mm)*		Cut-off value†	Sensitivity (%)	Specificity (%)
	Metastatic nodes	Non-metastatic nodes	Metastatic nodes	Non-metastatic nodes			
A	7 (1–18)‡	4 (1–10)	5 (1–15)	3 (1–5)	5	80	66
B	11 (2–22)¶	8 (1–15)	7 (1–20)	3 (1–10)	8	77	67
C	11 (1–22)§	10 (1–20)	6 (1–20)	5 (1–10)	10	61	73
D	10 (2–24)¶	7 (1–20)	6 (1–19)	3 (1–9)	8	61	73
E	9 (2–23)¶	6 (1–16)	5 (1–17)	4 (1–10)	6	65	72
F	11 (3–24)‡	7 (1–16)	6 (2–16)	5 (1–6)	6	69	57

*Values are mean (range). †Calculated by receiver–operator characteristic analysis. ‡*P* < 0.01, §*P* < 0.0001, ¶*P* < 0.001 versus non-metastatic nodes (Welch *t* test)

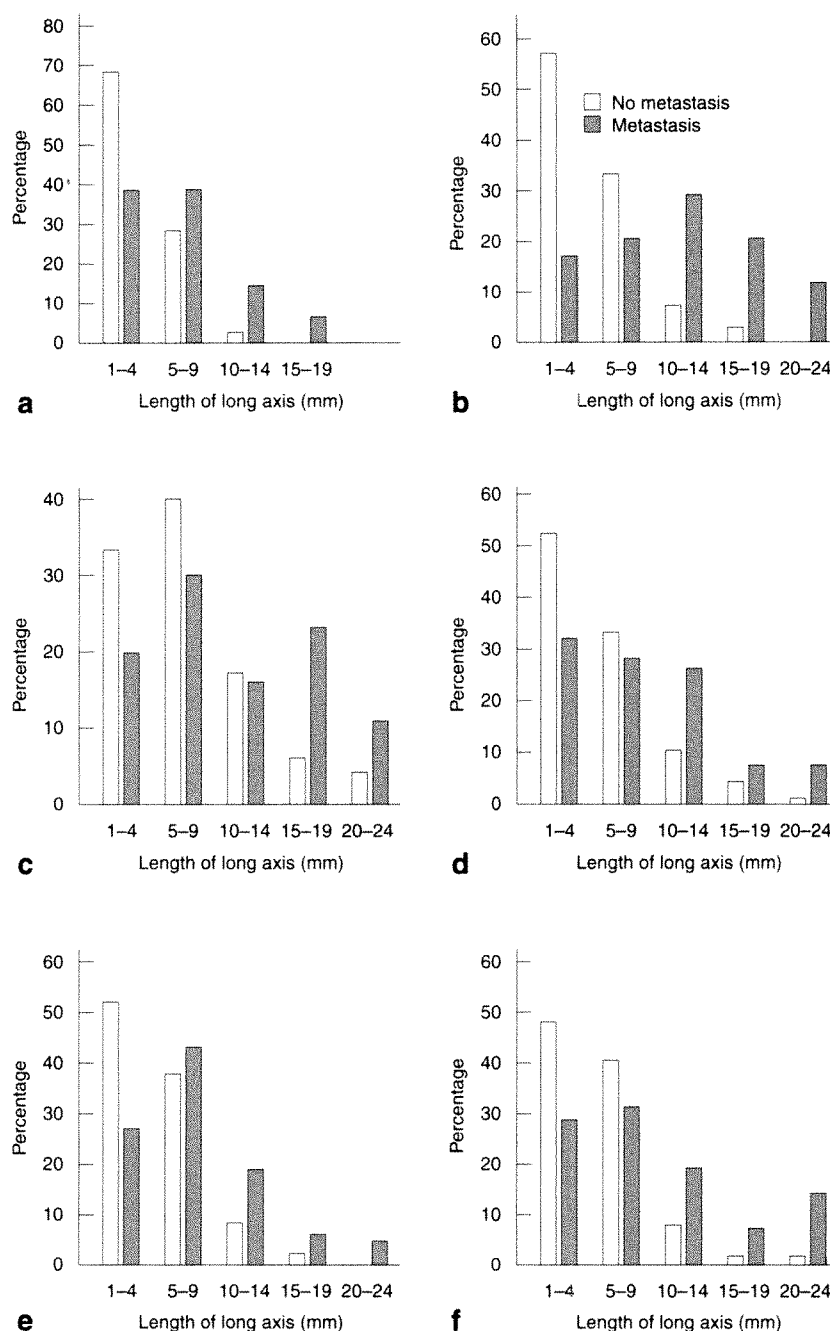


Fig. 1 Size distribution of nodes in each anatomical group: **a** group A ($n = 520$); **b** group B ($n = 718$); **c** group C ($n = 1336$); **d** group D ($n = 1770$); **e** group E ($n = 1981$); **f** group F ($n = 497$). Of nodes with metastasis, more than 50 per cent were 1–9 mm in diameter, excluding nodes in group B

included 46 in the neck, 257 in the mediastinum and 213 in the abdomen. The mean number of dissected lymph nodes was 55 per patient, comprising four neck nodes, 31 mediastinal nodes and 20 abdominal nodes.

The size of nodes with no evidence of metastasis was greatest at the tracheal bifurcation (10 mm), followed by the

pulmonary hilar nodes (8 mm). The cut-off size for the diagnosis of metastasis was 10 mm or less in all groups (*Table 2*). The size of the nodes was smallest in group A when compared with the other groups. In group A, 78 per cent of nodes with metastasis were smaller than 10 mm and 39 per cent were smaller than 5 mm (*Fig. 1*). As for the

Table 3 Node size: length ratio by size of node and tumour involvement

Node diameter	Size: length ratio	
	≥ 0.5	< 0.5
≥ 10 mm (n=1520)		
Involvement	156 of 266 (59)	110 of 266 (41)
No involvement	407 of 1254 (32)	847 of 1254 (68)
< 10 mm (n=5302)		
Involvement	203 of 250 (81)	47 of 250 (19)
No involvement	4102 of 5052 (81)	950 of 5052 (19)

Values in parentheses are percentages. There were significant correlations between the presence or absence of node involvement and shape in nodes 10 mm or more in diameter ($P < 0.005$, χ^2 test)

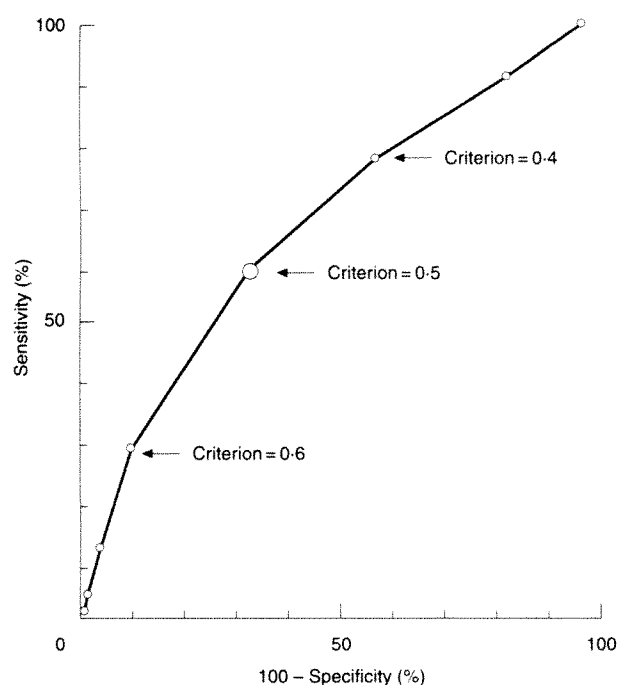


Fig. 2 Receiver–operating characteristic analysis of the shape of nodes 10 mm or greater for the diagnosis of metastasis. The sensitivity and specificity correlated with a criterion were plotted. The point that offers the highest sensitivity and specificity simultaneously was regarded as the criterion for the diagnosis of metastasis (○). The size: length ratio was defined as the short axis divided by the long axis of each lymph node, and served as an index of the shape of the node. A value 0.5 or more was considered spherical

relationship between the shape and the presence of node metastasis, overall 81 per cent of nodes less than 10 mm in diameter had an S:L ratio of 0.5 or more (Table 3). Of the 1520 nodes 10 mm in diameter or larger, the criterion for

the diagnosis of metastasis was 0.5 with a sensitivity of 58 per cent and a specificity of 68 per cent by ROC analysis (Fig. 2).

Discussion

Because of the high incidence of recurrence in the cervical and superior mediastinal lymph nodes after oesophagectomy for oesophageal cancer, lymph node dissection of the neck, mediastinum and abdomen has been recommended and practised in Japan since the mid-1980s^{12–15}. The effect of this resection on survival remains controversial, but the extent of lymph node metastasis and its relationship to survival were more accurately determined by this extended lymphadenectomy. It was found that intra-thoracic oesophageal cancer metastasizes extensively to nodes in the neck, mediastinum and abdomen once the oesophageal tumour has invaded the submucosal layer or deeper. The extent of lymphatic metastasis is a more important factor in the prediction of survival than the depth of invasion of the primary oesophageal tumour^{4–7}. Careful evaluation of lymph node metastasis is of vital importance in deciding the therapeutic strategy for patients with intra-thoracic oesophageal cancer. Patients are usually evaluated before operation by mediastinal and abdominal CT, ultrasonography of the neck and endoscopic ultrasonography. Node metastases are usually diagnosed by their size on CT or by endosonographic features^{14–21}; however, there have been no studies on the relationship between the size of a node and the incidence of metastasis, nor is there a reliable criterion for estimating the presence of metastasis in the node.

Kiyono *et al.*²² reported that the standard for the maximum size of a normal node was largest (12 mm) at the tracheal bifurcation and smallest (7.3 mm) at the pulmonary ligament in a study of 40 cadavers. Glazer *et al.*²³ investigated the number and size of normal mediastinal lymph nodes by CT in 56 patients with disorders not influencing the mediastinal nodes. They detected nine nodes in each patient and concluded that 10 mm was the threshold for normality. These studies, however, did not yield sufficient information about normal nodes because lymph nodes may not be physiological at autopsy and small nodes are not detected by CT.

In the present study, fresh lymph node specimens were obtained at operation and evaluated macroscopically. A mean of 55 nodes was obtained in each patient by extended lymphadenectomy. Although the cervical region is rich in nodes, the mean number of nodes removed was small. The mean size of nodes at each site was lower than that reported previously^{22,23}. A likely explanation is that all lymph nodes were resected, even small ones, and that patients with

advanced disease, who might have had larger nodes, were excluded. The size of nodes without metastatic disease varied according to the location. The tracheal bifurcation nodes were the largest, followed by the pulmonary hilar nodes in the mediastinum. Kiyono *et al.*²² and Glazer *et al.*²³ have reported similar results. The size of involved nodes was larger than that of uninvolved nodes in each group. Therefore, node size can be used as a criterion for estimating the presence of metastases, but the difference in the size of the nodes by location should be considered.

Nodes 10 mm or more in diameter and 5 mm or more can be detected by CT and ultrasonography respectively. Group A and F nodes are defined as M category by the classification of the Union Internacional Contra la Cancrum²⁴. The preoperative diagnosis of metastasis in these nodes would be helpful in determining the potential for curative surgery. For nodes in group F, 6 mm was the cut-off value for the diagnosis of metastasis, with a sensitivity of 69 per cent and a specificity of 57 per cent, but the diagnostic value was lowest among the six groups. When a coeliac or common hepatic artery node is detected by CT, the node harbours metastatic disease 88 per cent of the time. For nodes in group A, 5 mm was the cut-off value for the diagnosis of metastasis, with a sensitivity of 80 per cent and a specificity of 68 per cent. Cervical nodes should be investigated by ultrasonography; CT is too insensitive for these nodes. For group D and E nodes, the cut-off value for the diagnosis of metastatic disease was 8 and 6 mm respectively. The sensitivity was low in these groups. Nodes in groups D and E, however, can be dissected while the oesophagus is mobilized and the stomach is prepared for reconstruction. Conversely, dissection of group B and C nodes requires meticulous and careful surgical techniques. The complete dissection of these nodes is occasionally associated with an increased incidence of recurrent laryngeal nerve palsy and pulmonary complications. Therefore, the correct preoperative diagnosis of metastasis in these nodes might avoid some morbidity.

For group B nodes, 8 mm was the cut-off value for the diagnosis of metastasis, with a sensitivity of 77 per cent and a specificity of 67 per cent. The sensitivity of a 10-mm cut-off value was only 60 per cent, although the incidence of metastasis to one or more of these nodes in each patient was high (30 per cent). Therefore, there is a relatively high rate of false-negative nodes when lymph node metastases are diagnosed by CT. The sensitivity improves to 92 per cent when 6 mm is taken as the cut-off value for lymph node involvement. To reduce the false-negative rate, the recurrent laryngeal nerve nodes could be investigated by endoscopic ultrasonography. The cut-off value was greatest (10 mm) for group C nodes. Tracheal bifurcation nodes tended to be aggregated. When the capsule of each node was

not delineated clearly, the measured size of the node may be overestimated, and therefore the incidence of metastasis increased if the cut-off value is followed strictly.

Following ultrasonographic analysis of 126 lymph nodes, Tohnosu *et al.*²⁵ reported that metastatic lymph nodes are round (S:L ratio 0.5 or more) whereas normal nodes have an ellipsoidal shape (S:L ratio lower than 0.5). Surgeons know empirically that nodes appear to become spherical when metastasis is present. In this study, among the nodes smaller than 10 mm in diameter, 81 per cent had an S:L ratio of 0.5 or more, regardless of the presence or absence of metastasis. For nodes with a diameter of 10 mm or more, an S:L ratio of 0.5 or more was the cut-off value for the diagnosis of tumour involvement. Nodes with metastasis were significantly more likely to be spherical. ROC analysis revealed that nodes became more spherical as the incidence of metastasis increased, although this was associated with a lower sensitivity.

Sensitivity is low when lymph node metastasis is diagnosed by CT, although CT is well tolerated by patients. Endoscopic ultrasonography, which is less accepted by patients than CT and can be limited by strictures in the oesophagus, potentially has a higher sensitivity than CT for the diagnosis of lymph node metastasis. Evaluation of the size of nodes in addition to their endosonographic features may add to the specificity of endoscopic ultrasonography.

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Natural history of patients with adhesive small bowel obstruction

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Background: Small bowel obstruction (SBO) is a major cause of morbidity and financial expenditure. The goals of this study were to determine factors predisposing to adhesive SBO, to note the long-term prognosis and recurrence rates for operative and non-operative treatment, to elicit the complication rate of operations and to highlight factors predictive of recurrence.

Methods: The medical records of all patients admitted to one hospital between 1986 and 1996 with the diagnosis of SBO were reviewed retrospectively. This included 410 patients accounting for 675 admissions.

Results: The frequency of previous operation by procedure type was colorectal surgery (24 per cent), followed by gynaecological surgery (22 per cent), herniorrhaphy (15 per cent) and appendicectomy (14 per cent). A history of colorectal surgery (odds 2.7) and vertical incisions (odds 2.5) tended to predispose to multiple matted adhesions rather than an obstructive band. At initial admission 36 per cent of patients were treated by means of operation. As the number of admissions increased, the recurrence rate increased while the time interval between admissions decreased. Patients with an adhesive band had a 25 per cent readmission rate, compared with a 49 per cent rate for patients with matted adhesions ($P < 0.004$). At the initial admission 36 per cent of patients were treated surgically. Patients treated without operation had a 34 per cent readmission rate, compared with 32 per cent for those treated surgically (P not significant), a shorter time to readmission (median 0.7 *versus* 2.0 years; $P < 0.05$), no difference in reoperation rate (14 *versus* 11 per cent; P not significant) and fewer inpatient days over all admissions (4 *versus* 12 days; $P < 0.0001$).

Conclusion: The likelihood of reobstruction increases and the time to reobstruction decreases with increasing number of previous episodes of obstruction. Patients with matted adhesions have a greater recurrence rate than those with band adhesions. Non-operative treatment for adhesions in stable patients results in a shorter hospital stay and similar recurrence and reoperation rates, but a reduced interval to reobstruction when compared with operative treatment.

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Introduction

Small bowel obstruction (SBO) remains a leading cause of hospital admission. One study found that over 3 per cent of all emergency surgical admissions to a general hospital were secondary to SBO¹. The morbidity and financial cost of SBO are compounded by the recurrent nature of the disease. In a review of the clinical significance of adhesions, over 24 years, intestinal obstruction accounted for 0.9 per cent of all admissions, 3.3 per cent of major laparotomies and 28.8 per cent of cases of large or small bowel obstruction². In

1992 a British survey reported an annual total of 12 000–14 400 cases of adhesive intestinal obstruction. In 1994, in the USA, abdominal adhesiolysis for intestinal obstruction was responsible for 846 415 inpatient days at a cost of US\$1.3 billion³. These data emphasize the importance and enormity of the clinical problem. The natural history and risk factors, such as type of operation, timing and recurrence rate of adhesive obstruction, remain poorly described and stimulated the present audit.

The goals of the study were to determine the factors predisposing to adhesive SBO, to note the long-term

prognosis and recurrence rates for operative and non-operative treatment, to elicit the complication rate of operations, and to highlight factors predictive of recurrence.

Patients and methods

The medical records of all patients hospitalized between January 1986 and December 1996 with the discharge diagnosis of 'bowel obstruction' were reviewed. Patients with the particular diagnosis of adhesive SBO were selected from this group. The aetiology of SBO was determined from clinical presentation, operative findings, radiological findings and review of reports of the surgeon assessing the patient. No distinction was made between complete and partial obstruction. Furthermore, all patients whose records indicated a previous admission to another hospital for SBO were excluded from the study ($n=42$). These exclusions were made to ensure that all necessary information regarding the patient would be complete. The cohort included 410 patients accounting for 675 admissions for SBO.

Patients' medical records were reviewed in their entirety, including admission notes, daily progress notes, radiology reports, operative notes and pathology reports. Data collected included the demographic profile of age and sex, length of stay, type of treatment, operative findings, postoperative complications, number of previous hospitalizations for SBO and the interval between hospitalizations. Information collected on patients' past surgical history included the number of previous laparotomies, type of laparotomy, type of surgical incision at laparotomy, and the interval between last laparotomy and current hospitalization for SBO. Patterns of recurrence of SBO as well as the nature and outcome of treatment were documented. These data were collected on to standardized forms and then transferred to a computerized database (Microsoft Excel; Microsoft, Redmond Washington, USA). All crude rates (e.g. recurrence, complications) were analysed with the comparison of proportion test, and the odds of developing matted *versus* single adhesions were compared with the test of single proportions (assumed 1000 people at risk). Because all the continuous data had skewed distributions, the medians are reported and different groups compared with the non-parametric Wilcoxon rank sum test. Data were analysed using SAS software (SAS Institute, Cary, North Carolina, USA). Survival analysis was determined with the product limit method.

Results

Several risk factors were reviewed with respect to the development of the adhesions.

Previous operations

The number of previous laparotomies at initial presentation for adhesive SBO was widely distributed: 43 per cent of patients presented with obstruction after one laparotomy, 28 per cent after two previous laparotomies, 11 per cent after three, 9 per cent after four or more, and 9 per cent of patients had undergone no previous abdominal surgery. Procedure-specific frequencies of previous laparotomies along with others in the literature are indicated in *Table 1*. Colorectal (24 per cent) and gynaecological (22 per cent) procedures were the most common. The data in *Table 1* represent the percentage of the total number of antecedent operations by type.

Timing

Examination of the interval between a patient's last laparotomy and initial presentation for adhesive SBO suggests that patients are never free of risk for postoperative adhesions. In this study, 5 per cent of patients presented with adhesive obstruction less than 1 month after their last abdominal operation, 23 per cent presented between 1 month and 1 year postlaparotomy, 30 per cent between 1 and 5 years, 11 per cent between 5 and 10 years, and 12 per cent between 10 and 20 years. Some 14 per cent ($n=56$) of patients presented more than 20 years after their last laparotomy. There is a difference in time from previous laparotomy to presentation with obstruction depending on the nature of the laparotomy. *Table 2* examines these differences for the cohort of patients with one previous laparotomy. For patients with a previous appendicectomy or herniorrhaphy, the interval to obstruction tended to be longer, with only 8 per cent presenting less than 1 year after operation.

Recurrence

Overall, 137 (33 per cent) of the 410 patients admitted initially with adhesive SBO were readmitted at a later date with the same diagnosis. The recurrence rate increased as the number of previous admissions increased (*Fig. 1*). For example, 45 per cent of patients (61 of 137) admitted twice with adhesive disease were later readmitted, compared with 50 per cent ($n=14$) of those admitted four times, and seven of nine patients admitted six times (χ^2 for linear trend = 14.9, $P<0.001$).

The interval between readmissions varied from 1 day to 32 years, with a median of 1 (mean 2.8) year between the first and second admission. The time interval between recurrences decreased as the number of admissions increased (*Fig. 1*).

Table 1 Antecedent operations in patients with adhesion formation*

Reference	Year	n	Colorectal (%)	Gynaecological (%)	Appendicectomy (%)	Biliary (%)	Gastroduodenal (%)	Miscellaneous (%)
Admissions								
Tanhiphat <i>et al.</i> ⁴	1987	266	6	15	34	0	17	28
Cox <i>et al.</i> ⁵	1993	144	27	15	30	12†		16
Seror <i>et al.</i> ⁶	1993	297	25	13	10	12	15	25
Present study	2000	675	24	22	14	13	3	24‡
Patients								
Cox <i>et al.</i> ⁵	1993	119	27	15	30	12†		16
Present study	2000	410	24	22	14	13	3	24‡
Operations								
Bevan ¹	1984	98	9	21	35	11	0	24
McEntee <i>et al.</i> ⁷	1987	60	25	25	25	5	3	17
Mucha ⁸	1987	154	24	11	8	7	7	43
Menzies and Ellis ⁹	1990	80	39	15	15	5	5	22
Cox <i>et al.</i> ⁵	1993	92	20	21	34	16†		9
Matter <i>et al.</i> ¹⁰	1997	190	23	14	25	9	15	14
Present study	2000	204	19	32	16	13	2	19

*Reported studies are grouped in three categories based on the numbers of admissions, patients and operations, because it is inappropriate to compare studies that do not present similar data. Studies that report data in more than one category are cited in their relevant category. The percentages were derived using the total number of 'antecedent operations' as the denominator, and therefore all rows add up to 100 per cent. This is not the same as the percentage of patients with small bowel obstruction and a history of that particular operation, as some patients had more than one operation, and some patients had not previously undergone abdominal surgery. †Combined biliary and gastroduodenal operations. ‡Of the 24 per cent in the miscellaneous category, 15 per cent represent previous herniorrhaphy

Table 2 Distribution of intervals between previous laparotomy and initial admission for adhesive small bowel obstruction for the cohort of patients who had undergone one previous laparotomy*

Procedure	No. of patients	Time from previous laparotomy to admission			
		< 1 year	1–5 years	> 5 years	Unknown
Colorectal	45	31%	33%	34%	2%
Gynaecological	50	28%	20%	52%	0%
Appendicectomy or herniorrhaphy	36	8%	22%	55%	15%
Gastrectomy or cholecystectomy	26	27%	35%	38%	0%

*Twenty patients with one previous laparotomy did not undergo any of these procedures. $P=0.096$ (χ^2 test for linear trend)

Type of adhesion

In 160 patients whose operative record clearly indicated the type of adhesion causing the obstruction, 85 patients (53 per cent) had multiple matted adhesions and 72 (45 per cent) were obstructed secondary to a single adhesive band. Three patients (2 per cent) had both multiple matted adhesions and an obstructive band, producing two distinct areas of obstruction.

The previous surgical profiles were different for the two groups. Patients with a single adhesive band had a median of 1.0 previous (mean 1.4) laparotomy, compared with a median of 2.0 (mean 2.0) previous laparotomies for the group with matted adhesions ($P<0.0005$). Twelve patients

with a single adhesive band had had no previous abdominal surgery, compared with four such patients in the multiple matted adhesion group.

In addition to the total number of previous laparotomies, the indication for laparotomy also differed between the two groups. Because the number of patients who underwent operation and who never developed adhesions was unknown, the absolute risk of adhesion development for each indication for laparotomy could not be calculated. However, *Table 3* shows the odds of developing matted *versus* single-band adhesions for each indication for operation. Patients who had undergone previous colorectal procedures had a greater tendency to develop multiple matted adhesions than to develop a single band (odds 2.7,

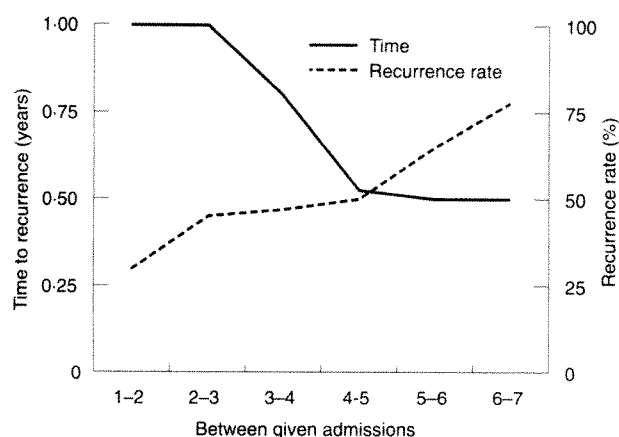


Fig. 1 Median time to recurrence for successive hospitalizations and recurrence rate for further episodes of small bowel obstruction. For example, the median time between the first and second admission was 1 year and that between the fifth and sixth admissions was 0.5 years. The recurrence rate for individuals with one episode of small bowel obstruction ($n = 137$) was 33 per cent and that for individuals with five episodes ($n = 14$) was 64 per cent

Table 3 Multiple matted adhesions *versus* single band for different indications for antecedent operation

	Multiple matted adhesions	Single band	Odds	P*
Colorectal	35	13	2.7	<0.001
Gynaecological	45	34	1.3	n.s.
Appendicectomy	24	16	1.5	n.s.
Cholecystectomy	21	13	1.6	n.s.

n.s., Not significant. *Test of single proportions

$P < 0.002$). Similarly, *Table 4* shows the type of adhesive disease relative to the type of previous incision.

The significance of the previous surgical and incisional profile is heightened when recurrence rates are considered for patients with the two types of adhesive disease. The median number of admissions per patient with a single obstructive band was 1.0 (mean 1.3), compared with a median of 2.0 (mean 2.4) admissions for patients with multiple matted adhesions ($P < 0.0001$). Furthermore, the readmission rate after operative treatment was 25 per cent for the single-band group compared with 49 per cent for the matted adhesion group ($P < 0.004$). *Fig. 2* shows the readmission rate profile in more detail. Only one (2 per cent) of 72 patients with a single band required more than two readmissions after operative treatment, compared with 15 (18 per cent) of 85 in the matted group ($P < 0.003$). At a later admission, 11 per cent (eight of 72) of patients in the single adhesive band group underwent reoperation compared with

Table 4 Multiple matted *versus* single band adhesions relative to previous surgical incisions

	Multiple matted adhesions	Single band	Odds	P*
Midline	69	32	2.2	<0.001
Paramedian	20	3	6.7	<0.001
Inguinal	10	9	1.1	n.s.
Transverse	13	14	0.9	n.s.
Subcostal	17	15	1.1	n.s.
McBurney	23	17	1.4	n.s.
Pfannenstiel	7	7	1.0	n.s.

n.s., Not significant. *Test of single proportions

14 per cent (12 of 85 patients) in the matted adhesion group (P not significant). The frequency of strangulated bowel was 18 per cent for operated patients with a single band and 16 per cent for operated patients with multiple matted adhesions (P not significant). The overall incidence of strangulated bowel was 6 per cent of admissions.

Treatment

Operative treatment was deemed necessary in 30 per cent of all admissions (36 per cent of first obstructions) with adhesive disease. Treatment usually entailed lysis of adhesions with or without small bowel resection. Of the 204 operations, there were 41 small bowel resections. The recurrence rate after small bowel resection at initial admission for adhesive SBO was 22 per cent, compared with 34 per cent after simple lysis of adhesions. The mean age of patients at initial admission was 63.1 years for those treated without operation and 60.1 years for those requiring operation. At the time of first obstruction, women had an operative rate of 42 per cent and men 29 per cent.

Recurrence rates were similar for patients treated with or without operation, regardless of whether it was the readmission was the first, second or third, etc. (*Fig. 3*). Although the total recurrence rates were similar, the cumulative frequency curve for the first readmission shows that patients treated conservatively tended to have earlier recurrence than those treated surgically (*Fig. 4*). For example, the probability of recurrence by 3 years post-discharge was 30 per cent for patients treated without operation, whereas surgically treated patients required 6 years to reach the same probability. Furthermore, the median time to readmission was 0.7 (mean 2.0) years for patients treated conservatively at initial admission compared with 2.0 (mean 4.3) years for those treated surgically ($P < 0.05$). The total number of cases of strangulation was 41 (6 per cent) of 675 admissions, 31 of which occurred on the first admission. During the first admission, eight (3 per cent)

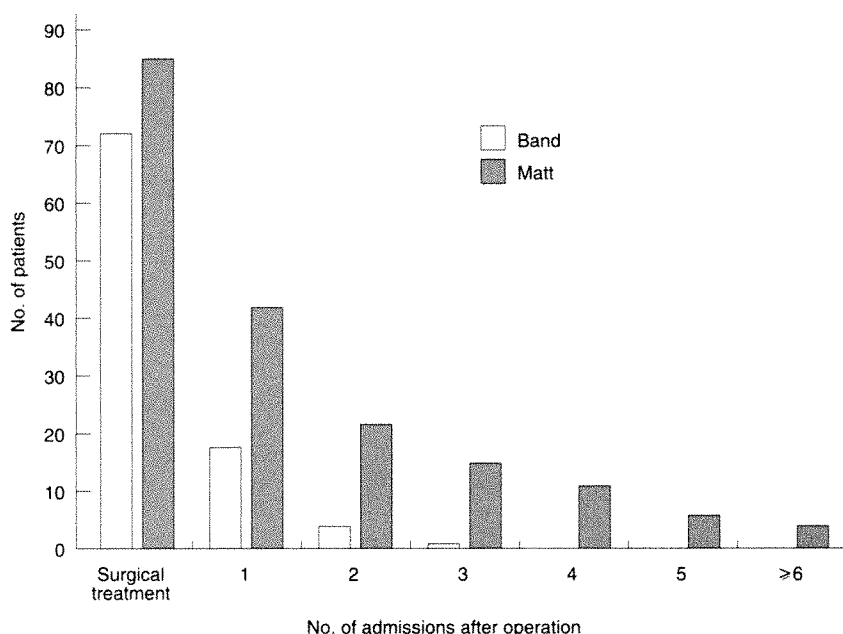


Fig. 2 The readmission pattern after operative treatment for single-band and multiple matted adhesions reveals a higher rate of recurrence in patients with matted adhesions. For example, of the 85 patients found to have matted adhesions at operation, 42 (49 per cent) experienced one readmission and 22 (26 per cent) were readmitted twice. In contrast, of the 72 patients with small bowel obstruction found to have an obstructive band at operation, 18 (25 per cent) were readmitted once and four (6 per cent) had two readmissions for adhesive disease. The higher recurrence rate for patients with matted adhesions was significant for the first four readmissions ($P < 0.05$, comparison of proportions test)

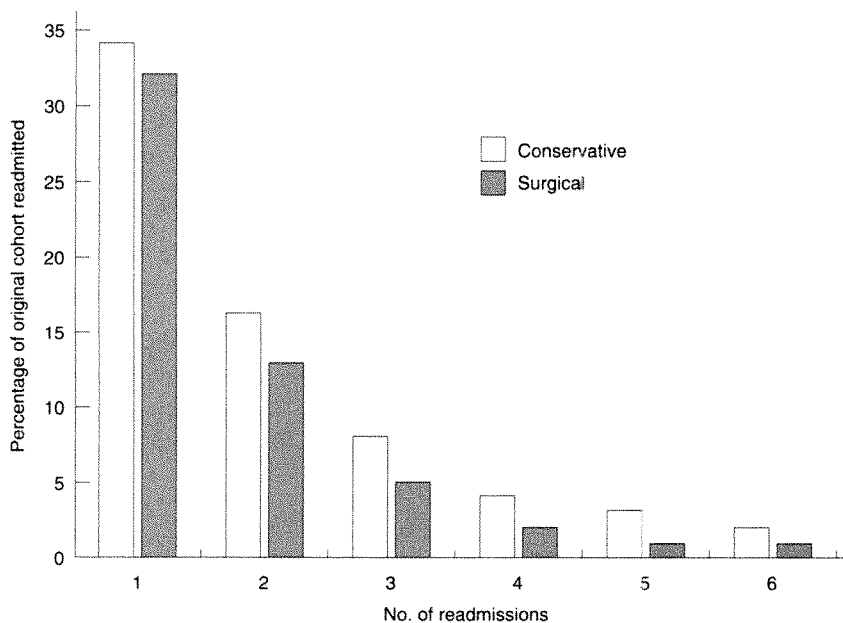


Fig. 3 Comparison of readmission rates over all subsequent admissions for patients treated conservatively or surgically at initial admission. Readmission rates are cumulative and do not account for variations in the length of follow-up. There were no significant differences between the two groups

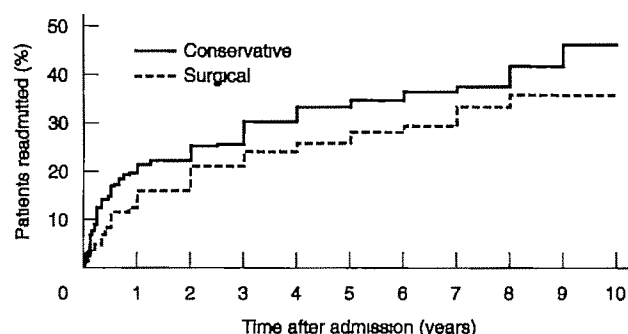


Fig. 4 Cumulative frequency of conservatively and surgically treated patients readmitted for bowel obstruction over time. Patients who were lost to follow-up or who died were censored from analysis. Because of the small numbers with a long follow-up and increasing standard error, the analysis was limited to a maximum of 10 years. There was a trend for conservatively treated patients to be readmitted sooner ($P < 0.1$). Log rank test

of the 267 patients treated without operation developed a later episode of strangulated bowel, compared with just one patient (1 per cent) of the 143 treated surgically. However, this difference was not statistically significant ($P = 0.23$). The median time from discharge following conservative treatment to readmission with strangulated bowel was 6 months (mean 1 year).

The median length of hospital stay for patients treated by operation was 12 days. For patients treated non-surgically the median stay was 4 days ($P < 0.0001$). Caution must be exercised in comparing these two lengths of stay because most patients who underwent operation usually had a trial period of non-operative treatment and therefore, by necessity, would have a longer length of stay.

Complications

The postoperative mortality rate was 3 per cent (six deaths). The postoperative complication rate for patients treated by operation for adhesive obstruction approached 18 per cent and included respiratory (six patients), cardiac (six), renal (nine), gastrointestinal (ten), wound infection (ten) and miscellaneous (six) complications. The mean age of patients who experienced postoperative morbidity was 66.6 years, significantly greater than that of patients treated by operation who did not experience complications (59.3 years) ($P < 0.04$).

Discussion

Previous laparotomies predispose to future intra-abdominal adhesions^{2,9-11}. In this series, 43 per cent of patients presented after one previous laparotomy and 28 per

cent obstructed after two laparotomies. In contrast, Cox *et al.*⁵ found that 77 per cent of patients presented after just one laparotomy. It is noteworthy that 9 per cent of the present patients had undergone no previous surgery.

Few studies have addressed the issue of the proportion of abdominal operations that result in adhesions. In an autopsy study of 752 cadavers, adhesions were found in 67 per cent of those who had undergone a previous operation but in 28 per cent of cadavers with no previous operation¹¹. In a prospective analysis of 210 patients undergoing a laparotomy who had previously had one or more abdominal operations, 93 per cent of patients had adhesions, compared with 10.4 per cent of 115 patients at first-time laparotomy who had asymptomatic adhesions⁹. The relative prominence of previous gynaecological operations in the surgical profile of the present patients with adhesion was higher than that in other studies^{5,8-10,12}. The incidence of postoperative SBO was reported to be 10.7 per cent at 64 months following appendectomy and 6.4 per cent at 67 months following cholecystectomy¹³. At autopsy, 47 per cent of patients who underwent only an appendectomy and 73 per cent of those who had only a cholecystectomy were found to have adhesions¹¹.

The interval between a patient's last laparotomy and initial admission for adhesions is widely distributed. Menzies and Ellis⁹ found that 21 per cent of patients presented less than 1 month after laparotomy, compared with just 5 per cent in the present series. Ellis² noted that a follow-up of more than 2000 laparotomies demonstrated that 1 per cent of patients developed adhesive obstruction within 1 year of operation, and half of these occurred within the first postoperative month. However, 20 per cent of cases appeared more than 10 years later. The time interval to obstruction tended to be longer after appendectomy and herniorrhaphy than after colorectal and gynaecological procedures. Cox *et al.*⁵ and Matter *et al.*¹⁰ reported similar findings.

The operative rate (30 per cent) for adhesive obstruction in the present study is in the low range when compared with that in most other series, which have reported operative rates ranging from 27 to 66 per cent^{4-8,10,14-20}. The strangulation rate, 6 per cent of all admissions and 20 per cent of operated cases, as well as the postoperative morbidity (18 per cent) and mortality (3 per cent) rates, were comparable to those in other recent series. Morbidity was age related, with the mean age of patients experiencing postoperative complications being 7.3 years greater than that of patients with no postoperative complications ($P < 0.04$). No distinction was made between patients with complete or partial obstruction, because clinical and radiological features depend on the time course and degree of obstruction⁴, and previous investigators found no

distinction in outcome or mortality between complete and partial SBO^{6,17}. Women had a higher rate of operation than men (42 *versus* 29 per cent). Of the 41 cases of strangulated bowel, 29 (71 per cent) occurred in women, 15 of whom had had a previous gynaecological operation.

The crude recurrence rate after initial admission for patients in the present series was 33 per cent overall, 32 per cent after operation and 34 per cent following conservative treatment. However, the crude recurrence rate is not an accurate reflection of the risk of recurrence because it fails to take into account the length of follow-up for each patient. To account for differences in follow-up times, survival analysis should be used (Fig. 4). The 5-year recurrence rate for surgically treated patients was 27 per cent, compared with 34 per cent for conservatively treated patients. Barkan *et al.*²¹ found a 5-year recurrence rate of approximately 20 per cent following operative and 40 per cent following non-operative treatment of initial episodes, whereas Landercasper *et al.*¹⁷ found a corresponding rates of 25 and 40 per cent respectively. They reported that 10 per cent of patients having operation and 17 per cent of those not undergoing operation ultimately required operation for SBO in an average follow-up of 4.4 years.

The similarity of recurrence rates for surgical and non-surgical treatment does not support the notion that operative management of an adhesive episode reduces the risk of reobstruction. However, the time interval to readmission varies significantly between operated (median 0.7 years) and non-operated (median 2.0) groups. A similar differential in interval to readmission was reported by Barkan *et al.*²¹. During a single admission in this study, the median stay was 8 days longer for patients having operation than for those treated conservatively (12 *versus* 4 days). Landercasper *et al.*¹⁷ reported an even greater differential (20 *versus* 8 days).

In the present series, as the number of previous admissions for SBO increased, the recurrence rate increased, and the time interval between recurrences decreased (Fig. 1). With more than three admissions for obstruction, the likelihood of recurrence increased to more than 50 per cent and the median time to recurrence fell to approximately 6 months. This trend was also found by Barkan *et al.*²¹ and reflects the intransigent nature of adhesive SBO.

The presence of an even distribution between single-band (46 per cent) and multiple matted (54 per cent) adhesions is similar to that in other series^{5,8}. Patients with a history of colorectal operations had the highest odds of developing multiple matted adhesions (odds 2.7, $P < 0.001$), as were patients with previous vertical incisions (odds 2.5, $P < 0.001$). Patients with matted adhesions have a median of 1.0 more admissions ($P < 0.0001$) and a 24 per cent greater

readmission rate ($P < 0.004$) than those with a band. Whereas recurrent obstruction is more likely with multiple matted adhesions, strangulation has been reported to occur more frequently in patients with a single obstructive band⁵. This has led Cox *et al.*⁵ to recommend that single-band adhesions be divided when found incidentally at laparotomy.

The management of patients with an acute episode of adhesive SBO remains controversial. No fixed rules regarding indications for or timing of operation are in place and the decision is ultimately at the discretion of the individual surgeon. At one extreme, some surgeons espouse immediate operative management^{2,22–25} in almost all cases, following the adage 'never let the sun set or rise on a SBO'. This belies the fact that more than 50 per cent of adhesive obstructions respond to non-operative treatment⁷. Recognizing the significant morbidity and mortality associated with the operative management of SBO, the surgeon would be remiss not to afford these patients the opportunity for spontaneous resolution. Cox *et al.*²⁰ concluded that, in the absence of any signs of strangulation, patients with adhesive SBO may be safely managed with non-operative treatment, with most cases resolving within 48 h of admission. Data from a number of studies have demonstrated that operative rates vary widely, from 27 to 66 per cent^{4–8,10,11,17–19,26–28}.

Other surgeons have found an initial non-operative trial period of bowel decompression to be more appropriate^{6,19,21,26,27,29,30}. The danger in non-operative management of the stable patient is the risk of bowel strangulation and subsequent increased mortality rate. In this study 40 (6 per cent) of 675 admissions had strangulated bowel at operation. Mucha⁸ reported strangulation to occur in 8 per cent of cases of adhesive SBO. Clinical indicators of impending strangulation have been found to be inconsistent and unreliable^{8,15,24,28,31}. The optimum length of a non-operative trial for patients with acute SBO is controversial. Reports range from a maximum of 12 h^{16,18,32} to 5 days⁶ of rehydration and bowel decompression before definitive operation becomes essential. Most reports set the limit somewhere between these two extremes^{4,7,14,15,20,32,33}.

Although data vary from report to report, the burden of caring for patients with admissions for adhesive SBO is enormous. The cost of time and injury is incalculable for the extra time and injury caused to organs encountered during operations not related to adhesive disease but in which adhesiolysis is an essential component of an operation to gain access to the part of the abdomen required for the planned procedure. The magnitude of the problem highlights the need to continue investigations into ways to prevent and control the development of this pernicious and ubiquitous problem.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Changes in pancreatic resection for chronic pancreatitis over 28 years in a single institution

Sir

Falconi *et al.* (*Br J Surg* 2000; 87: 428–433), described a large series of patients with chronic pancreatitis undergoing resection and reported that pain relief was obtained in the majority of patients, exocrine insufficiency was seen in almost all patients and endocrine insufficiency was seen in 72% of the 69 surviving patients with a median follow up of 10 years.

Autologous islet transplantation is particularly attractive for patients who require pancreatic resection for chronic pain. One of the major problems in isolating pancreatic islets has been the lack of a reliable collagenase preparation and impure solutions would cause the islets to fragment with a suboptimal yield. A new enzyme marketed as 'Liberase'® (Boehringer Mannheim, Inc., Indianapolis, USA) has significantly improved the isolation procedure. It is possible to obtain an adequate islet yield even from a severely fibrotic pancreas. The procedure of islet transplantation is a simple injection of cells into the liver via the portal vein after completion of pancreatectomy. The complications of injecting impure islet preparations, such as liver infarction, portal hypertension and DIC have not been a problem in recent experience.

Investigators from the University of Minnesota¹ reported 48 patients who received autologous islet transplants of whom 43 underwent total or near-total and five partial pancreatectomy. For their analysis of insulin-independence they excluded patients who underwent partial pancreatectomy, one who died and another who had pre-existing diabetes. Of the 39 patients, 51% were insulin-independent at least one month post-transplant and 34% were insulin-independent at 2 and 10 years, with no graft failing after 2 years. The group from the University of Leicester², performed 16 autologous islet transplants after total pancreatectomy with similar results. Investigators at Indiana University Medical Center performed six autologous islet transplants in patients with chronic pancreatitis and intractable pain after pancreatectomy³. Implantation and graft function was considered successful if C-peptide exceeded 0.50 ng mL⁻¹. The islet yield after purification was 402 000 equivalent islet number with an average purity of 67%. All recipients showed clear evidence of islet function but some required small amounts of insulin in the postprandial period (mean follow up of 5.5 months). Glycated haemoglobin remained within normal limits. Pain relief was sustained when patients received total pancreatectomy; near-total pancreatectomy resulted in recurrence of pain within 3 months.

Autologous pancreatic islet transplantation should be considered in all patients undergoing resection for chronic pancreatitis as the secondary complications of diabetes can be

devastating. Long-term follow up is required to study the duration of insulin independence.

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Prognostic significance of oestrogen receptor β in breast cancer

Sir

Since Speirs and Kerin (*Br J Surg* 2000; 87: 405–9) wrote their review, immunohistochemical data on ER β expression in breast cancer and its correlation with ER α , PgR and other prognostic factors has been published.

The association of ER β with ER α , PgR and other prognostic factors was studied in 92 primary breast tumours using immunohistochemistry¹ and 60% of tumours were ER β positive, with 76% of ER α positive and 76% of PgR positive tumours being positive for ER β , while ER α and PgR were positive in 87% and 67% of ER β positive tumours, respectively. When both ER α and PgR status were combined 77% of ER α positive/PgR positive tumours were found to be positive for ER β , only 22% of ER β positive tumours were negative for both ER α and PgR. In addition, ER β was found to be significantly associated with negative axillary node status, low grade and low s-phase fraction and that the overexpression of ErbB-2 was found to be significantly associated with ER β negative tumours. Similar significant associations were found with ER α status. This report based on protein expression is therefore at odds with RT-PCR based studies which have shown that ER β expression does not correlate with ER α expression², that coexpression of the two ER isoforms is associated with poorer prognostic factors³, and that ER β has an inverse relationship with PgR status⁴.

Currently no data exists on the independent prognostic value of ER β . Future studies must be directed at addressing this issue if the role of ER β in breast cancer is to be understood and if it is to be used routinely in clinical practice to guide treatment and predict outcome.

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- 1 Jarvinen TAH, Peltö-Huikko M, Holli K, Isola J. Estrogen receptor β is coexpressed with ER α and PR and associated with nodal status, grade and proliferation rate in breast cancer. *Am J Path* 2000; 156: 29–35.
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Pain after laparoscopic cholecystectomy

Sir

Drs Wills and Hunt (*Br J Surg* 2000; 87: 273–84) are to be congratulated for their extensive review but I would like to comment on two conclusions.

They stated that heated gas has been demonstrated to improve outcome. We published a randomized trial comparing heated with cold gas (not included in the review)¹ and our results were in contrast with those reported in the review, i.e. gas heating did not reduce pain after upper abdominal procedures.

The study endpoints reported by Korell *et al.*² showed conflicting data and the results are not applicable to gastrointestinal surgery. The study of Mouton *et al.*³ may be biased because the gas was both heated and humidified and one cannot draw conclusions about the respective efficacy of treatments. Furthermore, the methods in the latter trial did not allow blinding and there was no calculation of sample size. There is therefore currently no evidence to support the efficacy of gas heating to reduce pain.

The efficacy of intraperitoneal analgesic instillation was asserted in the review. We conducted a meta analysis evaluating this feature which was published in an abstract form⁴. We found no obvious benefit of analgesics when instilled during laparoscopic cholecystectomy. I agree with the authors that much work is needed to find the best way to prevent postlaparoscopy pain.

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- 1 Slim K, Bousquet J, Kwiatkowski F, Lescure G, Pezet D, Chipponi J. Effect of CO₂ gas warming on pain after laparoscopic surgery. A randomized double-blind controlled trial. *Surg Endosc* 1999; 13: 1110–4.
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Authors' reply

Sir

We thank Professor Slim for his comments. When we prepared our review we were not aware of his trial. We now share his reservations about heated gas, particularly as we have just completed a randomized trial of heated *versus* cold gas in patients having laparoscopic fundoplication and have shown no difference in favour of heated gas. We considered a meta-analysis concerning intraperitoneal local anaesthesia but decided that there were too many confounding variables to justify its use.

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Influence of gender on outcome from ruptured abdominal aortic aneurysm

Sir

Semmens *et al.* (*Br J Surg* 2000; 87: 191–4) report that, compared with men, women with ruptured abdominal aortic aneurysms are less likely to (a) be admitted to hospital (b) undergo emergency surgery, and (c) survive surgery. They have partially corrected for age by grouping patients in age bands, but it is likely that in each 10-year band the mean age for women was older than that for men.

Ageism and the biological consequences of old age probably contribute most to the different outcomes for men and women, but treatment selection is also important. Referral to hospital, deciding to operate and to continue with vigorous postoperative therapy are all discretionary. Life expectancy at birth in England and Wales is currently 5.5 years longer for

women than men¹. Women commonly marry older men and will usually be widows when they rupture their aneurysms. General practitioners, surgeons and anaesthetists tend to exercise their discretion to actively treat younger patients with a surviving spouse who are living independently. Doctors are encouraged in active management by a spouse at risk of loneliness and dependency, and discouraged by children with vested interests in avoiding the burden of a dependant parent and securing probate on their estate. Vascular surgeons practice in accordance with the prevailing ethos of the civilization in which they live.

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1 Annual abstract of Statistics 1999, the Stationery Office.

Letter 2

Sir

Semmens *et al.* have raised an interesting issue in evaluating risk factors for the outcome following rupture of abdominal aortic aneurysm (AAA). They found that women with a ruptured AAA are more likely to die than men as they studied this issue using the Western Australia Health Service Research Database.

In 1998 nationwide 581 patients underwent an emergency operation for ruptured infrarenal AAA in the Netherlands. Data were collected using the National Medical Registration Foundation, Landelijke Medische Registratie (LMR), SIG Health Care Information, Utrecht, The Netherlands. Though there were 509 men (87.6%) and 72 women (12.4%), the ages of the different sexes was comparable. The in-hospital mortality rate in women was 51.4 per cent, whereas in men this was 38.1 per cent. This difference in mortality rates between the sexes (13 per cent, 95 per cent confidence interval 0.9–25.6 per cent) is statistically significant.

Although the condition of AAA is more common in men, the outcome following rupture seems to be worse for women. Therefore the conclusion of increased awareness for an AAA in women is important as this may improve the outcome for this group.

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Authors' reply

Sir

The poorer outcome for women with AAA rupture compared to men were observed in each age-group and the figures speak

for themselves. The findings were also evident when the analyses were carried out for 5-year age groups, although these data were not reported in the paper. We are reassured to note the data from Holland supports the Western Australian findings. While the study is not able to provide causes for the poorer outcomes in women there are a number of factors worth considering. (1) The use of 'male' criteria, e.g. Maximum diameter, may increase the incidence of ruptured AAA in women and explain this finding. However, once rupture has occurred, this should not then influence outcome. (2) There is a lower index of suspicion for the diagnosis of ruptured AAA in women because it is less common; and (3) women who get AAA have had to work harder on their risk factors, e.g. smoking, and have greater comorbidities such as IHD.

The concept that women are not referred for treatment of their ruptured aneurysm, but allowed to die is an unexpected interpretation, especially on the grounds that they are widows and depressed, or that they have '...children with vested interests in avoiding the burden of a dependant parent and securing probate on their estate'. Mr Collin contends that this is 'the prevailing ethos' of practice by doctors and vascular surgeons in the United Kingdom. These reasons are unlikely to influence treatment practices in Western Australia where practice is streamlined to direct the patient to theatre as quickly as possible. We hope that the effect of 'the prevailing ethos' in the United Kingdom does not provide the impetus for a 'second fleet' consisting of elderly women to the shores of the antipodes.

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Reliability of sentinel lymph node biopsy for staging melanoma

Sir

I read with interest the article by Jansen *et al.* (*Br J Surg* 2000; 87: 484–9). I have also been involved in assessing the value of sentinel lymph nodes in patients with malignant melanoma and these nodes can be identified by blue dye with or without lymphoscintigraphy. Once the node has been detected, melanoma can be assessed histochemically or by combined immunohistochemical means. With this in mind I would be grateful if the authors could comment upon two questions:

1. Was there any correlation between histologically positive nodes and the different methods of detection of the sentinel node? Was the radioactive node more often histologically positive than the blue node or vice versa?

2. There were six patients with relapsed melanoma and on re-examination only one patient was found to have occult deposits (histologically and immunohistochemically). Would the authors recommend elective node dissections for patients with immunohistochemically positive nodes (S100 and HMB-45) in spite of negative histology? I have reviewed (unpublished) 79 patients with Stage 1 malignant melanoma at Gartnavel General Hospital, Glasgow, where the sentinel lymph node was detected by blue dye and combined methods and my findings were broadly similar to the authors' results.

Finally, although the state of sentinel lymph nodes is important, its role, as a prognostic indicator remains to be defined.

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Authors' reply

Sir

An interesting question is raised by Majumder. We did, however, not look for a correlation between the detection technique and the presence of metastases: the majority of sentinel nodes were both blue and radioactive, which makes such an analysis unreliable. In breast cancer patients, where almost half the sentinel nodes were either blue or radioactive, we found the following¹: 37% of sentinel nodes that were both blue and radioactive were tumour-positive, against 18% of nodes that were only radioactive and 49% of nodes that were only blue. This suggests that the blue dye is more specific for the detection of tumour-positive nodes. Regarding the second question: we do recommend completion lymph node dissection for patients with metastasis detected by immunohistochemistry only. We think that there is insufficient data to support a policy of removal of only the tumour-positive sentinel node. Breslow thickness or the surface area of the metastatic deposit may also be related to the presence of additional tumour-positive nodes. The value of each of these predictive factors has not yet been established.

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- 1 Doting MHE, Jansen L, Nieweg OE, Piers DA, Tiebosch ATMG, Schraffordt Koops H *et al.* Lymphatic mapping with intralesional tracer administration in breast carcinoma patients. *Cancer* 2000; **88**: 2546–52.

Some personal thoughts on plagiarism

Sir

I would like to respond to the letter from Dr Ng (*Br J Surg* 2000; **87**: 826)

I was the reviewer who 'discovered' the article which plagiarized my own. Dr Ng's notion that 'an appreciate part of the introduction had been copied' is imprecise. In truth, Dr Dalyan *et al.* copied my entire article-including references and tables. Dr Ng magnanimously suggests that 'if I were the reviewer I would get pretty excited at finding the validity of my original claim reaffirmed by further study and I would hasten to help rephrase the duplicated sentences, hoping that that the publication of their set of data would prove the reproducibility of mine'. I disagree. Words, when shaped into sentences, paragraphs, ideas, become the intellectual property of their original author. What the plagiarists did in this case is like taking one of Shakespeare's plays and copying it verbatim with only the names of the characters changed. Doing so is an intellectual crime. Would Shakespeare call the duplicators to offer them his help in rephrasing his own sentences? Dr Ng suggests that 'anyway, it takes much more time and effort to produce the statistics than literary presentation'. How wrong! How easy it is to generate some data and calculate statistics. How difficult it is to publish the work. I recommend that Dr Ng follow the current series on 'Surgical Publishing' in this Journal to realize that generating an idea, realizing it, and shaping it into a publishable manuscript is a most demanding task. Dr Ng goes further to claim that 'beside, the sentence structure can be changed while the data cannot'. Wrong again. Data can be falsified or simply fabricated.

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Changing patterns in the management of gastric volvulus over 14 years

Sir

We read with interest the article by Teague *et al.* (*Br J Surg* 2000; **87**: 358–61) reviewing the management of patients with gastric volvulus. From their study 29 patients presented acutely, which compares to our own audit of over 40 patients with a similar median age. The acute presentation was a rare

event and indeed many of the patients had accepted their symptoms as normal for many years. We congratulate them on the high percentage of laparoscopic repairs but found that the paraoesophageal hernia is frequently incarcerated with considerable inflammation at the axes of rotation that have necessitated open surgery. We also have a low threshold for splenectomy, particularly in the elderly when the spleen is intimately involved in the volvulus and hernia. The oesophagus is often friable and we have had to use the Thal patch technique to reinforce the oesophageal wall and prevent leaks from ischaemic tissues in some patients. Historically one of the major factors leading to the development of an organoaxial volvulus has been the mobility of the gastrocolic omentum and

the authors make no comment on the management of the transverse colon. Was colopexy used as part of the procedure?

Gastric volvulus is a rare condition and although laparoscopic surgery may benefit the very elderly in whom there is significant comorbidity, the laparoscopic technique needs to address the potential pitfalls that may be found.

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Surgical Emergencies. 1st ed.

J. Monson, G. Duthie and K. O'Malley (eds)

Pp. 406 Illustrated. 1999 Oxford Blackwell Science £75 00

This book is aimed at the trainee on acute surgical take, faced with a variety of emergency admissions and acute surgical problems. It provides an accessible source of essential information of use to the trainee, who may be faced with an unfamiliar clinical scenario, in particular at night, when access to more experienced personnel may not be readily available. It has been written by surgeons with specialist expertise in their respective fields and covers a wide range of general surgery topics ranging from advanced trauma life support to gastrointestinal bleeding and laparoscopy and laparotomy in the acute abdomen. Subspecialty topics have also been included, such as the management of urological trauma and the acute abdomen in pregnancy. Chapters dealing with shock, burns and life-threatening surgical infections are useful and informative. It is well laid out and illustrations are of a high standard. Each chapter includes highlighted boxes, which are particularly useful and which list the salient points of the topic under review. The layout also facilitates the book's use as a quick reference work. Suggestions for further reading have been included but the lists are not exhaustive, which reflects the primary aim of the book. Some repetition of topics does occur, but this serves to familiarize the trainee with different presentations and different aspects of management of common surgical problems. In conclusion, this book provides an excellent introduction for surgical trainees dealing with a variety of surgical emergencies. It is easily read, well-illustrated, informative and provides crucial core information.

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Ambulatory Anorectal Surgery

H. R. Bailey and M. J. Snyder (eds)

260 x 182 mm Pp 223 Illustrated. 2000 New York: Springer. £75.50

Ambulatory anorectal surgery is an interesting book for those who are contemplating starting an ambulatory practice. It gives in the first 80 pages, advice for the set up of both freestanding ambulatory centres and Hospital ambulatory centres, dealing with anaesthesia problems, postoperative management and prevention of urinary retention; it discusses the advantages and disadvantages of several patient positions. The next 120 pages contain descriptions of aetiology, diagnostics, operation techniques, and results of the treatment of haemorrhoids, fissures, anorectal abscesses, perianal and rectovaginal fistulas, condylomata, rectal prolapse, rectoceles

and local procedures for rectal cancer. This part contains nothing really new (it advocates outdated procedures such as anal dilatation, Thiersch wires and so on). To my surprise abdominal procedures for rectal prolapse are also discussed and the author also indicates that these are not feasible in an outpatient setting. Newer procedures for haemorrhoidal prolapse, such as the circular stapling technique, are not mentioned. This volume can only be recommended for those surgeons who have an interest in organizing day care facilities for anorectal surgery.

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Surgical Attending Rounds. 2nd ed.

K. F. Lee and C. Dyke (eds)

227 x 152 mm Pp 510 Illustrated. 1999. Philadelphia Lippincott Williams & Wilkins. \$39 95.

From the title, *Surgical Attending Rounds*, the authors set out to provide an insight into the management of surgical patients structured around key-questions faced in day-to-day clinical practice. Each chapter starts with a clinical vignette introducing the new topic, and questions invite the reader to organize knowledge in the way that is required when faced with real patients. By the end of each chapter both practical (e.g. clinical signs, investigations, follow-up and prognosis) and theoretical (such as pathogenesis) issues are covered, and the main points are summarized in a decision-making flow chart. This succession of questions and answers can prove to be the most efficient way of gaining confidence and a firm grounding during basic surgical training. The text might be easier to read if the emphasis (i.e. the use of bold and italic fonts) concentrated on the questions rather than on parts of the answer. The book should not be read instead of but rather after a more traditional textbook and answers should then be compared with those of the authors. This valuable exercise of formative assessment will convince the reader that applied knowledge is a new trend in medical education that can provide a more efficient and attractive way of knowledge acquisition. The book could become a valuable training tool before viva or clinical examination for surgical trainees preparing for examination.

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Vascular Surgery Highlights

H. Davies (ed)

210 x 148mm Pp 92. Illustrated. 2000. Oxford Health Press. £15.00.

I believe this is a relatively useful little book which describes succinctly where we appear to be standing with respect to the topics covered. Each section is concise; the key points are highlighted and there is a relatively useful list of references at the end of each section. My only concern is at whom this is precisely aimed. I suspect specialist registrars and the occasional vascular surgeon would find it useful. I would hope that vascular surgical specialists would have this sort of information already filed away in their own minds.

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Instant Anatomy. 2nd ed.

R. K. Whitaker and N. R. Boley

234 x 158 mm Pp. 205. Illustrated. 2000 Oxford: Blackwell Science £12.95

Any attempt to summarize the human anatomy in 200 pages of little more than A5 size is an achievement in itself. That it should be clearly written and well-illustrated indeed deserves congratulation. The main chapters of this second edition of *Instant Anatomy* cover arterial, venous, lymphatic and neurological anatomy. A common theme is adopted with well-drawn diagrams to the left and concise text to the right. I particularly like the absence of confusing clinical vignettes and

the minimal use of eponymous names which remain only as a source of amusement to elderly anatomists. Although the text is concise it is in places extremely detailed, and trainees and consultants in head and neck specialties will particularly appreciate the chapter on the cranial nerves.

Having started extremely well this little volume's performance tails off towards the finish. From Chapter 8 onwards the initial style of the book, with illustrations and associated text, is dropped. Chapter 8 is a summary of the muscular anatomy of the body and would be useful as a quick revision exercise if the muscles were listed in functional or regional groups, but it becomes unreadable because they are listed in alphabetical order. Likewise the exhaustive list of joints in Chapter 9 is indigestible. The next chapter contains an exhaustive list of the ossification centres and times which is probably more useful to the trainee radiologist than surgeon, but is none the less exhaustive. Chapters 11 and 12 which deal with the anatomical relations of foramina and spaces within the skull and remainder of the body, respectively, could only be useful if a standard anatomical text with excellent illustrations were open at the same time. The book gets back on course with the next chapter which gives a useful summary of the relation of various anatomical structures to the vertebral level, but finally peters out with a very brief excursion into the embryology of the branchial arches which is far too sketchy to be of use. Still, despite its failings this little text has much to commend it. As a quick revision reference for both undergraduate and post-graduate examinations, as well as an aide memoire for specialist registrars and consultants, I would still recommend it.

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Scientific Surgery

- Kent PJ, Maughan J, Burniston M, Nicholas T, Parkin A, Robinson PJ. Perforate-invagination (PIN) stripping of the long saphenous vein reduces thigh haematoma formation in varicose vein surgery. *Phlebology* 1999; 14: 43–7. Fourteen patients with bilateral veins had one leg stripped with the PIN and one with a conventional stripper. The amount of thigh haematoma measured by radiolabelled red blood cells was less after PIN stripping.
- Kingsnorth A, Porter CS, Bennett DH, Walker AJ, Hyland ME, Sodergren S. Lichtenstein patch or Perfix plug and patch in inguinal hernia — a prospective double blind randomized controlled trial of short term outcome. *Surgery* 2000; 127: 276–83. Some 141 patients were randomized. No information was given about hernia recurrence rates but the plug was 5 min quicker to insert, caused less postoperative pain, but was more expensive.
- Yoshioka K, Connolly AB, Ogunbiyi OA, Hasegawa H, Morton DG, Keighley MR. Randomized trial of oral sodium phosphate compared with oral sodium picosulphate (Picolax) for elective colorectal surgery and colonoscopy. *Dig Surg* 2000; 17: 66–70. A total of 153 surgical patients and 103 having colonoscopy were studied. Sodium phosphate produced superior preparation in both groups without affecting patient acceptability.
- Galizia G, Lieto E, Castellano P, Pelosio L, Imperatore V, Pignatelli C. Lateral internal sphincterotomy together with haemorrhoidectomy for treatment of haemorrhoids: a randomized prospective study. *Eur J Surg* 2000; 166: 223–8. Forty-two patients with prolapsed piles and high sphincter pressures were included. No patient became incontinent and results were improved by the addition of a sphincterotomy.
- Luck AJ, Hewett PJ. Ischiorectal fossa block decreases post-hemorrhoidectomy pain: randomised, prospective, double-blind clinical trial. *Dis Colon Rectum* 2000; 43: 142–5. Pain scores were lower for 24 h and analgesic requirement less in this study including 20 patients having day case surgery.
- Altomare DF, Rinaldi M, Milito G, Arcana F, Spinelli F, Nardelli N *et al.* Glyceryl trinitrate for chronic anal fissure — healing or headache. Results of a multicenter randomized, placebo-controlled, double-blind trial. *Dis Colon Rectum* 2000; 43: 174–9. The trial included 132 patients from nine centres. Side-effects were frequent and only 119 completed the trial. Healing rates at one month (44% after GTN and 52% after placebo) were similar, as were pain scores.
- Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K *et al.* Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; 88: 1082–90. Some 754 patients were included; treatment involved monthly pamidronate infusions for up to 24 months. Treatment reduced the risk of fractures and other skeletal complications (51 versus 64 per cent).
- Smith AJ, Nissan A, Lanoutte NM, Shi W, Guillem JG, Wong WD *et al.* Prokinetic effect of erythromycin after colorectal surgery: randomised placebo-controlled, double-blind study. *Dis Colon Rectum* 2000; 43: 333–7. Erythromycin failed to improve the duration of ileus or the length of hospital stay in this study of 150 patients undergoing surgery for colonic or rectal cancer.
- Leung KL, Lai PB, Ho RL, Meng WC, Yiu RY, Lee JF *et al.* Systemic cytokine response after laparoscopic-assisted resection of rectosigmoid carcinoma: a prospective randomized trial. *Ann Surg* 2000; 231: 506–11. Thirty-four patients were studied. Laparoscopic assistance reduced cytokine levels, both interleukin and C-reactive protein levels were lower than after open operation.
- Robson MC, Hill DP, Smith PD, Wang X, Meyer-Siegler K, Ko F *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; 231: 600–11. The study compared granulocyte colony stimulating factor and fibroblast growth factor alone, and in combination, against placebo. Cytokine-treated ulcers healed better than with placebo, fibroblast growth factor alone was best.
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- Kakkar VV, Howes J, Sharma V, Kadziola Z. A comparative double-blind randomised trial of a new second generation LMWH (Bemiparin) and UFH in the prevention of post-operative venous thromboembolism. *The Bemiparin Assessment Group Thromb Haemostas* 2000; 83: 523–9.13. Some 298 patients undergoing hip arthroplasty were included. Post-operative bleeding rates were similar but Bemiparin reduced the rate of venous thromboembolism from 18.7 per cent after unfractionated heparin to 7.2 per cent.

The British Journal of Surgery website can be found at www.bjs.co.uk. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about the website, either in writing or through the website address.

British Association of Endocrine Surgeons Abstracts

The following abstracts were presented at the Millennium Meeting of the British Association of Endocrine Surgeons held in conjunction with the American Association of Endocrine Surgeons and the Swedish Association of Endocrine Surgeons, in London and Lille on 22–25 May 2000.

The *British Journal of Surgery* prize was awarded to the abstract entitled 'Total parathyroidectomy in patients with chronic renal failure' by R. N. Saunders, R. Karoo, H. Y. Tiong, G. J. Murphy, M. Metcalfe, M. L. Nicholson.

Role of frozen section, sex, age and tumour size in differentiating follicular adenoma from carcinoma: a meta-analysis

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Background: Frozen section (FS) has been the mainstay of intraoperative decision-making in thyroid neoplasms for many years. However, since the widespread use of preoperative fine-needle aspiration, the need for FS in patients with follicular neoplasms (FNs) has been debated. Preoperative features may be better at distinguishing follicular carcinoma (FC) from adenoma (FA). One reason why these issues are unresolved is because clinical studies are often too small to reach statistical significance. The purpose of this study was to combine modern trials and use the technique of meta-analysis to determine the efficacy of FS and the role of sex, age and tumour size in patients with FNs.

Methods: Inclusion criteria were published and unpublished studies between 1990 and 1999 inclusive, in which patients had a permanent pathology (PP) diagnosis of FA or FC (including Hurthle cell tumours) and underwent FS or had clinical features recorded. A pooled sample of the combined data was analysed for the prognostic variables and outcomes. $P < 0.05$ was considered significant.

Results: Nineteen studies were included. FS was evaluated in 11 studies ($n = 2204$). FS matched PP in 82 per cent of patients and was considered helpful. FS was indeterminate in 13 per cent of cases and was considered unhelpful. FS was detrimental in 4 per cent of patients. In 27 per cent of FCs, FS reported FA (false negative) and in 1 per cent of FAs, FS reported FC (false positive). Overall, FS had an 87 per cent sensitivity, 48 per cent specificity, 92 per cent positive predictive value, 35 per cent negative predictive value and 82 per cent accuracy. Clinical features were examined in ten studies ($n = 1980$). Nine studies ($n = 1780$) reported sex; 20 per cent of patients were male. A disproportionately high percentage of patients with FC were male (28 per cent) compared with female ($P < 0.001$). Two studies ($n = 548$) reported age; 36 per cent of patients were over 50 years old. A disproportionately high percentage of patients

with FC were aged over 50 years (52 per cent) compared with those younger than 50 years ($P < 0.001$). Six studies ($n = 1620$) reported tumour size; 19 per cent of FNs were larger than 3–5 cm. A disproportionately high percentage of FCs were larger than 3–5 cm (33 per cent) compared with smaller lesions ($P < 0.001$).

Conclusion: FS is able to differentiate FC from FA in over 80 per cent of patients. It has a false-positive rate of less than 1 per cent and therefore may be trusted most when it reports a FC. In cases in which FS reports FA, male sex, age greater than 50 years and tumour size larger than 3–5 cm can be used as indicators that a FN will be a FC.

Screening for genetic aberrations in papillary thyroid cancer using comparative genomic hybridization

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Background: Papillary thyroid carcinomas (PTCs) are a heterogeneous group of neoplasms that display a wide variability in clinical behaviour. Knowledge of the genetic composition of these tumours may help improve prognostication, but is currently limited. The aim of this study was to identify the genetic composition of pathologically low-risk papillary thyroid cancers and identify differences based on age, using a powerful, genome-wide analytical technique, comparative genomic hybridization (CGH).

Methods: Tumour samples from patients with pathologically confirmed well differentiated PTC, less than 4 cm in size and without extrathyroidal extension or distant metastasis, were procured from the institutional tumour bank. CGH analysis was performed by differentially labelling tumour and normal DNA with fluorescent agents. The labelled DNAs were coprecipitated and simultaneously hybridized to normal metaphase chromosomes on glass slides. After chromosomal segregation, computerized image analysis was performed to detect fluorochrome intensity along the entire length of each chromosome. The ratio of fluorescent signal intensity was used

to identify the presence of genetic abnormalities. Statistical age-group comparisons of the CGH findings were performed using Fisher's exact test.

Results: Genetic abnormalities were detected in ten of 21 cases. A recurrent pattern of aberrations was identified, involving losses at chromosomes 1p, 9q, 17, 19 and 22, and gains at 4, 6 and 13. The prevalence of CGH-detectable aberrations was not influenced by age, but loss of chromosome 22 was unique to patients aged less than 40 years ($P = 0.05$) and was associated with a higher rate of locoregional metastasis (19 *versus* 80 per cent; $P = 0.02$).

Conclusion: Two distinct patterns of genetic composition were observed in PTC. One group had no detectable abnormalities, while the other had a recurrent pattern of gains and losses that localized to identical chromosomal loci. Although a divergent pattern of involvement was seen in younger patients, the direct clinical significance of this finding needs to be elucidated. Moreover, the identified pattern of alterations suggests that novel oncologically consequential genes are present within the involved loci. Molecular cloning of the genes at each of these sites is warranted.

Hypothyroidism following hemithyroidectomy: Incidence, risk factors and management

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Background: Hypothyroidism is often an unrecognized sequela of hemithyroidectomy. The purpose of this study was to determine the incidence, risk factors and management of hypothyroidism occurring after hemithyroidectomy for nodular thyroid disease.

Methods: All euthyroid patients who underwent hemithyroidectomy from 1992 to 1999 were evaluated for age, sex, preoperative and postoperative serum thyroid-stimulating hormone (TSH) levels, pathology and follow-up. Time of diagnosis and therapeutic doses of thyroid hormone were determined for patients with hypothyroidism. Patients who underwent completion thyroidectomy and those who were on thyroid hormone before operation for TSH suppression or after operation for prevention of recurrent disease were excluded.

Results: During the study period, 70 euthyroid patients underwent hemithyroidectomy. Postoperative hypothyroidism was diagnosed in 25 (36 per cent) with a mean(s.d.) TSH level of 8.51(6.53) (units l⁻¹). Hypothyroidism was subclinical in 16 and overt in nine patients. There were no significant sex or age differences between hypothyroid and euthyroid patients. The mean(s.d.) preoperative serum TSH level was 1.94(1.00) (units l⁻¹ in patients diagnosed with postoperative hypothyroidism compared with 1.08(0.75) (units l⁻¹ in euthyroid patients ($P < 0.05$). Associated lymphocytic thyroiditis was

present in ten of 25 hypothyroid patients compared with ten of 45 euthyroid patients ($P > 0.05$). Nineteen patients received thyroid hormone treatment in doses varying from 0.5 to 1.9 (mean 1.3) g kg⁻¹. Follow-up varied from 1 month to 7 years (mean 1 year). All but one hypothyroid patient was diagnosed within 2 months of surgery.

Conclusion: Postoperative hypothyroidism occurs in 36 per cent of patients following hemithyroidectomy. It is usually asymptomatic, and can be diagnosed early after surgery. Hypothyroid patients have higher preoperative TSH levels than euthyroid patients and treatment is accomplished with lower than normal replacement doses of thyroid hormone.

Role of antiapoptotic genes in genetic control of programmed cell death in Hashimoto's thyroiditis

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Background: In Hashimoto's thyroiditis (HT) thyroid cells die by apoptosis, programmed cell death. In addition to the reported abnormal Fas expression on thyrocytes, a decreased expression of the Bcl-2 antiapoptotic genes has also been demonstrated in thyrocytes. The ratio of the expression of death antagonists (e.g. Bcl-2 and Bcl-XL) to death agonists (Bax, Bak, Bcl-Xs and Bad) appears to determine the survival or death of thyrocytes under both physiological and pathological conditions.

Methods: The constitutive expression of Bcl-X was investigated in thyroid cells from ten multinodular goitre (MNG), ten Graves disease and four HT samples by immunofluorescence, confocal microscopy and Western blotting. The effect of proinflammatory cytokines (interferon (IFN) γ , tumour necrosis factor (TNF) α and interleukin (IL) 1 on Bcl-X expression on cultured thyrocytes was also studied.

Results: By *in situ* staining, an overall decreased Bcl-X expression was observed within the thyrocyte compartment in HT samples in comparison to that seen on thyrocytes from ten samples of MNG thyroid. Intrathyroidal lymphocytes were positive for Bcl-X. These findings were quantified using confocal microscopy which demonstrated an intensity of Bcl-X staining in MNG twice that of HT specimens. The ten specimens of Graves disease showed an intermediate and patchy staining on thyrocytes. *In vitro* studies have confirmed constitutive Bcl-X expression both by flow cytometry and Western blotting analysis with the latter showing a 27-kDa signal in all samples that corresponds to Bcl-XL. IFN- γ , alone and in combination with TNF- α and IL-1, decreased Bcl-X expression on thyrocytes.

Conclusion: HT thyrocytes underexpress Bcl-X whereas intrathyroidal lymphocytes have been found to be positive. It is

proposed that the decreased Bcl-X expression on thyrocytes of HT glands occurs as a result of proinflammatory cytokine release by infiltrating activated lymphocytes. The overall impairment of antiapoptotic gene protection may contribute to the susceptibility of HT thyrocytes to apoptosis.

Heat-stable plasma constituent responsible for caspase activation in Hashimoto's thyroiditis

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Background: Autoimmune thyroid disease is characterized by a spectrum of thyroid activity, with Graves disease (GD) and Hashimoto's thyroiditis (HT) at the extremes of over and under activity respectively. Hypothyroidism in HT is caused by apoptotic thyrocyte death, which is achieved via a cascade of cysteine protease (caspase) activity. It is still unclear whether thyrocyte death is the result of caspase activation secondary to extrinsic Fas/FasL interaction with the activation of procaspase 8 and/or of cytochrome C release from thyrocyte mitochondria consequent to impaired expression of the *Bcl2/Bcl-X* thyrocyte survival genes. This study was designed to clarify whether plasma constituents have a role in thyrocyte apoptosis and whether differential apoptotic kinetics can be observed in thyroid diseases.

Methods: Cultured thyrocytes from fresh surgical specimens were incubated with 5 and 20 per cent plasma from patients with multinodular goitre (MNG), GD and HT for between 5 and 180 min. Procaspase 8, caspase 3 and cytochrome C activities were monitored using Western blotting on thyroid lysates. Procaspase 8 was also studied microscopically using light microscopy and immunofluorescopy. To ascertain the role of complement activity in the induction of apoptosis, thyrocytes from MNG, GD and HT thyroids were also exposed to heat-treated plasma (56°C for 45 min) for varying time intervals before caspase 8 estimation.

Results: Western blot and immunofluorescopy confirmed that human plasma induces procaspase 8 in thyrocytes; Western blots also showed activation of cytochrome C and caspase 3 in these cells. At 30 min and up to 90 min thyrocyte procaspase 8 expression and the expression of breakdown products of this protein appeared to be more marked in the thyrocytes treated with HT plasma than MNG and GD plasma. Procaspase 8 expression was not altered by the heat of plasma. Thyrocytes exposed to plasma of patients with autoimmune and non-autoimmune conditions showed similar bands for caspase 3 and cytochrome C. The cytochrome C signal was stronger in the cells exposed to HT plasma at 30 min.

Conclusion: A heat-stable constituent of human plasma induces programmed cell death in thyrocytes. Plasma from

patients with HT appears to induce a greater death stimulus than that from patients with other thyroid conditions. Fas/FasL interaction appears to be involved in apoptotic thyrocyte death. The role of mitochondrial cytochrome C in the induction of cell death is unclear.

Expression of the *RET* proto-oncogene and the *RET/PTC* oncogenes in papillary thyroid carcinomas and its correlation to clinical manifestations

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Background: Papillary thyroid carcinoma (PTC) is the commonest thyroid cancer. It has an excellent prognosis if the patients receive appropriate treatment. However, a subgroup of patients with PTC develop distant metastases and eventually die from the disease. There are considerable difficulties in identifying such patients before operation, and there is a need for better tools to do so. Genetic changes, such as expression of the oncogenic fusion proteins *RET/PTC* 1–5, have been described but their correlation with the clinical picture and prognosis is unclear.

Methods: Sixty-one PTCs (50 primary and 11 recurrent tumours) from 61 patients were selected and analysed for expression of the *RET* tyrosine kinase domain (*RET-TK*) and the oncogenes *RET/PTC* by reversed transcribed polymerase chain reaction, followed by restriction enzyme digestion and direct sequencing. This expression was then correlated with clinical features of lymph node metastasis, distant metastasis, poor differentiation, tall cell variant, extrathyroidal growth, previous external radiation, recurrent disease and death from disease.

Results: Thirty PTCs (49 per cent) showed expression of *RET-TK*. Thirteen of them appeared to express wild-type *RET*, as upstream exons were also expressed. Three were explained by *RET/PTC* expression: one *RET/PTC1*, one *RET/PTC3* and one with a unique variant of *RET/PTC3*, previously only described in a patient with PTC from Chernobyl. Poor differentiation, but no other histopathological parameter, was significantly correlated with the expression of wild-type *RET*. Furthermore, in PTCs from 15 patients with a poor clinical outcome (death from disease or distant metastases) *RET-TK* expression was found significantly more often.

Conclusion: Half of the PTCs showed expression of *RET-TK*. Surprisingly, only three of them could be explained by known

RET/PTC oncogenes. Probably, some of the PTCs express wild-type *RET* while others could be explained by new, or not yet identified, *RET/PTC* rearrangements. Regardless of the mechanism for *RET*-TK expression, this seems to be correlated with a poor prognosis. If this holds true in a larger sample, *RET*-TK expression could be used as an additional marker to identify patients with PTC who have a less favourable prognosis, and who may benefit from more extensive treatment.

Thyroid transcription factor 2 gene expression in thyroid malignancy

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Background: Expression of thyroid-specific proteins such as thyroglobulin is controlled by several transcription factors. Thyroid transcription factor (TTF) 2 is the most recently characterized and has a temporal expression during thyroid embryogenesis suggesting a role in initiating differentiation. Studies on other thyroid-specific genes have shown a gradual loss in differentiation as a tumour progresses, although a good marker to distinguish follicular adenoma from follicular carcinoma is still needed. There is no information on TTF-2 expression in varying thyroid pathologies. Given its central role in thyroid differentiation, reverse transcriptase-polymerase chain reaction (PCR) was used to investigate this in both archival and fresh thyroid tissues and fine-needle aspirates.

Methods: Thyroid tissue was obtained with informed consent, snap frozen, and total RNA and messenger RNA (mRNA) was extracted. Since TTF-2 has no introns in the coding region, it was necessary to use mRNA. The RNA was reverse transcribed using oligo(dT) and MMV reverse transcriptase. The quality of the complementary DNA (cDNA) was verified by PCR using intron-exon boundary spanning primers for the phosphogluco kinase (PGK) housekeeping gene; a 250-base pair (bp) product is derived from cDNA but a 650-bp product from amplification of contaminant genomic DNA. PCR amplification of TTF-2 used two sets of primers; A + D spans the DNA-binding region and gives a product of 460 bp while primers P + E generate a product of 370 bp in the carboxyl end of the coding region. Products were analysed by agarose gel electrophoresis and compared with a 100-bp ladder.

Results: A single band of 250 bp was obtained in all 33 thyroid tissue samples but in only three of eight fine-needle aspirates, after 40 cycles, using the PGK primers. Appropriate size products were obtained, after 30 cycles, invariably with both sets of TTF-2 primers, in all 18 benign thyroid nodules of varying pathology, including all five follicular adenomas, and in five of 15 malignant thyroid nodules. Four of five papillary carcinomas and one of seven follicular carcinomas expressed

TTF-2; neither of two anaplastic carcinomas and one other carcinoma did not. One of six benign and one of two malignant thyroid nodules expressed TTF-2 on fine-needle aspiration cytology.

Conclusion: The results suggest loss of TTF-2 expression in poorly differentiated thyroid tumours and that TTF-2 may be helpful in distinguishing follicular adenoma from follicular carcinoma.

Prognostic significance of *RET* and *NTRK1* rearrangements in sporadic papillary thyroid carcinoma

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Background: The genetic background of papillary thyroid carcinoma (PTC) has been elucidated by the identification of somatic translocations of the tyrosine kinases *RET* and *NTRK1*. Expression of *RET/PTC* chimeras has been demonstrated in 10–25 per cent of sporadic PTCs while rearrangements of *NTRK1* were detected less frequently. Based upon the limited data available, some investigators have hypothesized that *RET/PTC* activation is preferentially associated with slow growing tumours of low malignancy in elderly patients, while other studies support the contrary.

Methods: Tumour tissues from 115 patients with sporadic PTC were harvested at operation and snap frozen. Following RNA extraction, expression analysis of the *RET* proto-oncogene as well as the *NTRK1* gene was performed by multiplex reverse transcriptase-polymerase chain reaction. Samples with suspected rearrangements of the genes were further analysed for expression of the hybrid messenger RNAs *RET/PTC1* to *RET/PTC4*, and for known *NTRK1* chimeras. Clinical data of all patients were documented in an extensive database of thyroid carcinomas maintained by this research group.

Results: Twenty-one (18 per cent) of 115 tumour samples revealed somatic rearrangements of *RET* while translocations of the *NTRK1* gene were demonstrated in 2 per cent of all samples analysed to date. The mean age of all patients was 52 (range 14–86, median 54) years and that of patients positive for *RET* rearrangements was 49 (range 14–82, median 49) years. Nine of 21 *RET*-rearranged tumours showed aggressive behaviour with locally invasive tumour growth and infiltration of adjacent structures such as muscles, vessels and trachea. Tumour samples without detectable *RET* translocations were associated with organ-exceeding tumour growth in only 20 per cent of cases.

Conclusion: These data represent one of the most comprehensive studies on gene translocations and their clinical significance in PTC. In accordance with international publications,

an incidence of 2 per cent of *NTRK1* rearrangements and 18 per cent of *RET* translocations is reported, which is in contrast to other national reports of low rearrangement rates. Somatic translocations were associated with tumours demonstrating aggressive behaviour in almost half of patients with PTC in all age groups, indicating a prognostic role of oncogenic *RET*/*PTC* activation.

Thyroid cancer management in North Trent. Case record review confirms the need for specialist care

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Background: The Calman–Hine Report mandates the need for specialist care of patients with cancer within the UK. The next round of accreditation will include an assessment of care available to patients with thyroid cancer. The Joint Thyroid Cancer Clinic in Sheffield allows secondary and tertiary referral to a multidisciplinary specialist team for the two million people of North Trent.

Methods: A retrospective case record review of the last 159 patients referred to the clinic by specialist and non-specialist surgeons was performed to assess surgical and pathological aspects of care, including preoperative, perioperative and postoperative management, as well as operative morbidity.

Results: A total of 37 surgeons at ten hospitals were involved in the initial management of 128 women and 31 men (mean age 53 (range 10–99) years) with thyroid cancer (111 differentiated, nine medullary, 16 anaplastic, 15 lymphoma, eight others), including 23 general surgeons (69 patients), ten ear, nose and throat surgeons (ten patients) and three specialist endocrine surgeons (66 patients). Non-specialist surgeons carried out 78 reoperative procedures. Histopathological review after referral by a specialist pathologist resulted in a change in diagnosis in 10 per cent of 125 patients (13 cases). Operation-specific surgical morbidity was recorded as follows:

	No. treated	Vocal cord palsy	Hypoparathyroidism
Non-specialist surgeons	85	9 (11)	16 (19)
Endocrine surgeons	66	3 (5)	5 (8)

Values in parentheses are percentages

Cancer Registry data indicated that a further 101 patients with thyroid cancer were never referred to the Joint Thyroid Cancer Clinic during the same period.

Conclusion: In North Trent, despite the presence of a long-standing and well established clinic, many patients with thyroid cancer do not receive specialist/multidisciplinary care. Patients

are often treated by surgeons with little experience of thyroid cancer, and the rates of inaccurate pathological diagnosis and operative morbidity are unacceptably high in patients treated by non-specialist teams.

Multicentre study comparing aggressive behaviour of familial non-medullary thyroid carcinoma and sporadic thyroid cancer

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Background: Familial non-medullary thyroid cancer represents about 5 per cent of all thyroid cancers of follicular cell origin. Whether familial non-medullary thyroid cancer is more aggressive than sporadic thyroid cancer is controversial.

Methods: Each patient with familial non-medullary thyroid cancer was matched with three controls for age, sex and tumour node metastasis (TNM) stage of disease. Possible prognostic factors were compared in relation to recurrence, metastases and mortality rate in both groups. Univariate analysis was performed using contingency table analysis and McNemar's χ^2 test for paired measurements. Multivariate analysis was used to evaluate factors significant in univariate analysis.

Results: Forty-eight cases (ten men) and 144 matched controls (30 men) were analysed with a mean follow-up of 102 and 94 months respectively. The mean age was 39 years for cases and 46 years for controls. Some 29 per cent of the cases and 12 per cent of the controls had history of prior or coexistent benign thyroid disease ($P < 0.05$). Ninety-four per cent of cases and 90 per cent of controls had papillary cancers; the remainder were Hurthle cell cancers. Based on TNM staging, there were 66 per cent stage I, 21 per cent stage II and 13 per cent stage III tumours in the familial non-medullary thyroid cancer group; the distribution was similar in the control group. Modified radical neck dissection was performed in 42 per cent of cases and 22 per cent of controls. Multifocal or bilateral disease was seen in 75 per cent of cases and 41 per cent of controls ($P < 0.05$); 35 per cent of cases and 16 per cent of controls had at least one recurrence ($P < 0.05$). Ten per cent of cases and 2 per cent of controls developed distant metastases ($P < 0.05$). Six per cent of cases but no controls died from thyroid cancer ($P < 0.05$). In patients with familial non-medullary thyroid cancer aged over 45 years ($n = 14$), distant metastases affected four, of whom three died. In multivariate analysis, age was the only significant variable that affected the disease outcome ($P < 0.01$).

Conclusion: Familial non-medullary thyroid cancer is more aggressive than sporadic thyroid cancer and is associated with

increased recurrence, metastasis and death, especially in patients over 45 years of age.

Primary hyperparathyroidism in India

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Background: Primary hyperparathyroidism (PHPT) in Indians has some unique clinical features, such as early age of onset, extreme osteopenia, crippling bone involvement, large parathyroid tumours, higher proportion of malignancy and severe, prolonged postparathyroidectomy hungry bone syndrome. The current study aimed to study (1) whether these features of PHPT in Indians are due to a variant form of PHPT and (2) pathogenetic factors of such variant disease.

Methods: Clinical, investigative and pathological features of 29 consecutive patients with PHPT (24 females, five males) who underwent parathyroidectomy at 13–60 (mean 38) years of age were reviewed. Spearman's correlation coefficient was calculated between serum calcidiol levels and biochemical variables, bone mineral density (BMD) before surgery and parathyroid tumour weight.

Results: Median duration of symptoms was 2.5 (range 1–26) years. Mean total serum calcium, iPTH and ALP levels were 12.4 mg dl^{-1} (normal $8.5\text{--}10.8 \text{ mg dl}^{-1}$), 955 pg ml^{-1} (normal $9\text{--}55 \text{ pg ml}^{-1}$) and 850 units l^{-1} (normal $35\text{--}125 \text{ units l}^{-1}$) respectively, while mean(s.d.) serum calcidiol and calcitriol concentrations were $14(6) \text{ ng ml}^{-1}$ and $52(29) \text{ pg ml}^{-1}$ (*versus* $9(9)$ and $30(14) \text{ pg ml}^{-1}$ in matched controls). All patients had symptomatic osteitis fibrosa cystica and eight were bedridden. Single or multiple spontaneous fractures occurred in 14 patients, brown tumours in 20, and long bones were barely visible on plain films in four. BMD z-scores at distal radius and lumbar spine (mean) were -4.2 and -3.8 . Palpable parathyroid tumours occurred in 14 patients and nine had renal damage, mainly nephrocalcinosis. Parathyroidectomy invariably resulted in long-standing severe hypocalcaemia, necessitating intravenous calcium infusion for 6 days on average, and long-term oral calcium and vitamin D supplementation. The mean parathyroid gland weight was 8.6 (range $2\text{--}36.6$) g and signs of carcinoma were found in four. There was a negative correlation ($P < 0.05$) between serum calcidiol and serum iPTH, and serum ALP and parathyroid gland weight.

Conclusion: PHPT in Indians manifests as severe, symptomatic musculoskeletal and renal disease. In spite of the severe hyperparathyroidism, the serum calcium levels are only moderately raised. These patients have signs of rapid parathyroid tumour growth resulting in large adenomas and a high proportion of parathyroid carcinomas. The signs of rapid

cell proliferation, excessive calcium insensitivity of PTH release and peripheral PTH resistance may clarify roles of widely prevalent vitamin D deficiency in pathogenesis of this variant of PHPT.

Surgery for primary hyperparathyroidism

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Background: Routine open bilateral neck exploration without preoperative localization or intraoperative parathyroid hormone assay has been repeatedly challenged over recent years as the optimal surgical strategy for the treatment of idiopathic primary hyperparathyroidism (HPT). This has prompted a review of the Oxford experience with adherence to traditional practice, questioning whether results could have been improved upon or cost justified by targeting unilateral exploration and immediate hormonal assay.

Methods: The records of all patients undergoing first-time surgery for idiopathic primary HPT over a 32-year period have been reviewed. In every patient bilateral neck exploration was performed and an attempt made to identify all four parathyroid glands. All macroscopically enlarged glands were removed and the operating time recorded. A successful outcome was defined as normocalcaemia without any therapy at 3-month review after surgery, with good cosmesis.

Results: Between 1968 and 2000, 688 patients were operated upon; a total of 2520 parathyroids were identified, of which 968 were abnormal. A single adenoma was found in 542 patients (79 per cent) (eight in a fifth gland), multiple gland disease in 120 (17 per cent) and parathyroid carcinoma in ten (1 per cent). Mean operating time for all patients was 65 min, including those requiring thyroid lobectomy and cervical thymectomy. When a single adenoma was found in a normal anatomical site the mean operating time was 35 min. Some 672 patients (98 per cent) were treated successfully.

Conclusion: Open bilateral neck exploration and removal of all macroscopically enlarged parathyroid glands resulted in a high level of success in this series. No evidence has been found in a worldwide literature search to suggest that expensive high technology would have provided greater benefit for the group as a whole.

Metabolic abnormalities and treatment of mild asymptomatic primary hyperparathyroidism

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Background: Primary hyperparathyroidism (pHPT) is associated with increased morbidity and mortality rates, especially

due to cardiovascular disease. This may be an effect of metabolic alterations in lipoprotein, glucose and urate turnover. The few previous reports studying this matter have been inconclusive and have included only hypercalcaemic patients.

Methods: In a population-based screening of 5202 postmenopausal women, 109 were diagnosed with mild pHPT. Some 92 patients, together with matched controls, were investigated to analyse metabolic disturbances, and the effect of parathyroidectomy and hormone replacement therapy (HRT). Sixty-nine pairs completed the 5-year study.

Results: Patients had higher serum calcium and parathyroid hormone levels than controls. They had hypertriglyceridaemia and a significantly increased amount of triglyceride-rich lipoproteins. Furthermore, patients had pronounced hypercholesterolaemia, although the level of high-density lipoprotein-cholesterol was lower, and higher serum blood glucose and urate levels. While 5 years of surveillance only failed to affect these alterations, parathyroidectomy with or without addition of HRT normalized the metabolic changes. Thus, 4 years after surgery no differences were seen between cases and controls.

Conclusion: The metabolic alterations in mild pHPT span over many extraparathyroid metabolic systems and constitute an increased risk of cardiovascular disease and death. Parathyroidectomy has a reversing effect on these proatherosclerotic changes, while surveillance does not affect the outcome. Even in mild pHPT surveillance may be questioned.

Prospective case-control analysis of treatment of menopausal primary hyperparathyroidism: calcium and parathyroid hormone

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Background: Therapeutic options in primary hyperparathyroidism (HPT) have not been analysed in postmenopausal women recruited by population-based screening.

Methods: Postmenopausal women ($n = 92$) with HPT detected at population-based screening entered into a prospective case-control comparison at mean(s.d.) 66.5(6.0) years of age. Biochemical signs of HPT were mild (mean(s.d.) serum calcium 2.59(0.14) mmol l⁻¹) and cases were considered overtly asymptomatic. Parathyroid surgery, oestrogen replacement therapy (ERT; ethinyloestradiol), ERT and surgery, and conservative surveillance were evaluated after 1, 2 and 5 years. Follow-up was complete in 75 per cent of the patients.

Results: Parathyroid surgery rendered the total and ionized calcium, and intact parathyroid hormone (PTH) values in blood, and the urinary calcium excretion indistinguishable between cases and controls. ERT was maintained during approximately 80 per cent of the follow-up period. It reduced

the blood calcium levels significantly and tended to increase the serum PTH level. Significant discrepancies, however, persisted towards the controls. ERT added no significant changes to the biochemical outcome of parathyroidectomy. Conservatively treated cases had essentially stable parameters over the study period.

Conclusion: Parathyroidectomy was the only treatment option that normalized basic variables of the calcium homeostasis to control levels in postmenopausal women with mild primary HPT.

Surgery versus surveillance of pancreaticoduodenal endocrine tumours in multiple endocrine neoplasia type 1

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Background: Management of pancreaticoduodenal endocrine tumours remains controversial in multiple endocrine neoplasia type 1 (MEN1). The authors' experience with MEN1-related pancreaticoduodenal tumours has been reviewed in order to evaluate a rational therapeutic approach.

Methods: Twenty-one patients with MEN1 with pancreaticoduodenal endocrine tumours were analysed with special regard to outcome of surgery and surveillance. In addition, a phenotype/genotype analysis was performed based on *MEN1* gene mutation analysis.

Results: Twelve of 21 patients had multiple tumours. Nine patients had gastrinomas, six non-functioning tumours, three insulinomas, two insulinomas and gastrinomas, and one had a vipoma. Six tumours were malignant with lymph node metastases (five gastrinomas, one vipoma). Seventeen patients were treated initially by either pancreatic left resection with tumour enucleation of the duodenum and/or pancreatic head ($n = 9$), tumour enucleation alone ($n = 7$) or pylorus-preserving partial pancreatectomy (PPPD; $n = 1$). Sixteen of 17 patients were cured biochemically after initial surgery and 11 remained free of disease after a median follow-up of 55 (range 2–197) months. Six patients underwent reoperation for recurrence and/or lymph node metastases, including two PPPDs in patients with gastrinoma. All six patients remained asymptomatic and three remained biochemically free of disease. Three of the 17 operated patients died from either unrelated causes ($n = 2$) or postoperative complications ($n = 1$). On the other hand, four asymptomatic patients with either gastrinomas ($n = 2$) or non-functioning tumours ($n = 2$) were closely surveyed and showed no progress or metastases on somatostatin (SMS) scans and computed tomography after 9–110 months. The genotype/phenotype analysis revealed that

patients with truncating nonsense or frameshift *MEN1* gene mutations in the N- or C-terminal regions (exons 2, 9 or 10) had a significantly higher rate of malignant tumours (55 *versus* 8 per cent; $P=0.04$) and tended to have shorter disease-free intervals (28 *versus* 120 months; $P=0.11$) than patients with other mutations.

Conclusion: An aggressive surgical approach is justified for pancreaticoduodenal tumours in patients with *MEN1* since symptom-free long-term survival can be achieved. However, *MEN1* gene mutations in exons 3–8 seem to be associated with mild behaviour of pancreaticoduodenal tumours which might allow close surveillance in asymptomatic patients with *MEN1*.

Helix-loop transcription factor, Id1, is overexpressed in medullary thyroid cancer

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Background: The helix-loop transcription factor (Id1) protein inhibits differentiation, enhances cell proliferation and is required for cell-cycle progression. Id1 is highly expressed in a variety of tumour-derived cell lines, increases following mitogenic stimuli and is overexpressed in some human neoplasms. It was therefore reasoned that the *Id1* gene may play a role in medullary thyroid carcinogenesis.

Methods: Id1 protein expression in human medullary thyroid cancer (MTC) and corresponding normal thyroid tissue was determined by Id1 immunohistochemistry. Calcitonin immunohistochemistry was used to determine the cellular localization of Id1 immunostaining. In a well characterized human MTC cell line (TT), the effects of growth stimulation (with serum) and redifferentiation (with phorbol esters) on Id1 expression were determined by Northern blot analysis.

Results: Id1 immunostaining intensity in MTC ($n=9$; six sporadic MTCs, two familial MTCs and one multiple endocrine neoplasia type 2A MTC) was moderate to strong whereas in the corresponding normal thyroid tissues ($n=9$) it was absent or faint in the C cells and follicular cells. Id1 immunostaining was significantly higher in MTC than the corresponding normal thyroid tissue based on the percentage of positive cells and immunostaining intensity ($P=0.002$, rank sum test). The 1.2-kilobase Id1 transcript was expressed in the TT cell line under basal culture conditions. Interestingly, Id1 messenger RNA (mRNA) expression was markedly upregulated (4.0 fold) following growth stimulation with 10 per cent fetal bovine serum. In addition, phorbol ester (which is known to induce redifferentiation of the TT cell line) downregulated Id1 mRNA expression in the TT cell line.

Conclusion: Id1 is overexpressed in MTC. Furthermore, increased Id1 expression is associated with an enhanced proliferative potential in MTC. The inappropriate proliferation and dedifferentiation of the C cells that lead to MTC, at least in part, may be regulated by the *Id1* gene.

Identification of a novel glucose transporter in medullary thyroid carcinomas and phaeochromocytomas

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Background: The authors previously reported that medullary thyroid carcinomas (MTCs) and phaeochromocytomas avidly take up the glucose analogue fluorodeoxyglucose (FDG) on FDG positron emission tomography. It was also shown that these tumours do not express any of the known human glucose transporters (Glut 1–5), which are responsible for glucose and FDG uptake into cells. It was hypothesized that a novel glucose transporter is responsible for glucose uptake in MTCs and phaeochromocytomas.

Methods: Using protein sequences from the known human glucose transporters (Glut 1–5), the National Center for Biotechnical Information expressed sequence tag database was screened for novel homologous sequences. Clones derived were used to screen a pooled kidney complementary DNA (cDNA) library, and cDNAs identified were used to identify patterns of expression by Northern blot analysis.

Results: A novel member of the human glucose transporter family, called Glut X2, was identified. This transporter had 33 per cent protein sequence identity to Glut 3. Hydrophobic analysis showed exofacial and transmembrane domain structure consistent with a hexose transporter. Northern blot analysis showed expression of GlutX2 in all seven MTCs studied, all three phaeochromocytomas and in TT cells, an MTC cell line. These tumours did not express any of the other known facilitative glucose transporters (Glut 1–5).

Conclusion: A novel member of the human glucose transporter family has been identified which may be responsible for glucose uptake in MTCs and phaeochromocytomas.

Randomized controlled trial of standardized meal stimulation for the detection of enteropancreatic endocrine tumours in patients with multiple endocrine neoplasia type 1

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Background: Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterized by the occurrence of hyperparathyroidism (approximately 100 per cent), and pituitary (approximately 40 per cent) and enteropancreatic endocrine (approximately 70 per cent) tumours. It has been suggested previously that serum pancreatic polypeptide and serum gastrin after standardized meal test stimulation are useful indicators for early identification of enteropancreatic tumours in MEN1. Therefore the usefulness of the meal test was evaluated in a screening programme of MEN1 mutation carriers.

Methods: In a prospective, controlled trial between September 1997 and December 1995, 55 standardized meal stimulation tests (563 kcal) were performed in 13 MEN1 mutation carriers with no evidence of enteropancreatic tumours (group 1); ten patients with MEN1 with histologically, biochemically and radiologically evident enteropancreatic tumours (group 2); and in 28 healthy adults for control (group 3). Genetic analysis was done by single-strand conformation analysis and direct sequencing. Serum pancreatic polypeptide and serum gastrin levels were measured by radioimmunoassay (Ideon, Sweden). Data were analysed using analysis of variance (Kruskal–Wallis test, 2 d.f.) and Mann–Whitney test.

Results: Median (range) basal serum pancreatic polypeptide levels were 214 (38–897) pg ml⁻¹ in group 1, 126 (13–263) pg ml⁻¹ in group 2 and 73 (13–357) pg ml⁻¹ in group 3. Median (range) serum gastrin levels were 103 (37–391), 551 (25–4080) and 65 (17–198) pg ml⁻¹ respectively, but gastrin levels in group 2 were strongly influenced by patients with known gastrinoma. Levels of both variables increased after meal stimulation in all groups. However, there was no significant difference between the groups after stimulation ($P > 0.05$).

Conclusion: Standardized meal stimulation test does not reliably indicate the presence of enteropancreatic endocrine tumours in patients with MEN1. It is not therefore used in the authors' routine screening programme for patients with MEN1.

Multiple endocrine neoplasia type 2A c804 RET mutation as an indication for prophylactic thyroidectomy

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Background: Missense mutations in five exons of the *RET* proto-oncogene have been found to cosegregate with the inherited cancer syndrome, multiple endocrine neoplasia type 2A (MEN2A). Sequence abnormalities involving c804 in exon

14 occur rarely and to date have been found in five kindreds. Initial reports linked the c804 mutation to a mild C-cell disease phenotype with low penetrance and an indolent course, and questioned the appropriateness of aggressive strategies such as prophylactic thyroidectomy in early childhood. The purpose of this study is to report the clinical correlates of five additional MEN2A kindreds that harbour the c804 *RET* mutation, with the intention of clarifying therapeutic recommendations in asymptomatic carriers.

Methods: Thirty-eight members from five distinct kindreds at risk for the c804 mutation underwent genetic analysis using genomic DNA and direct DNA sequencing. Operative and pathology reports were reviewed. Detection of C-cell hyperplasia (CCH) or medullary thyroid carcinoma (MTC) was accomplished biochemically by baseline or pentagastrin-stimulated calcitonin determinations.

Results: Twenty-three gene carriers were identified. The predisposing c804 missense mutation in each case resulted in a TTG, ATG or CTG substitution. Of the 23 patients testing genetically positive, 14 proceeded to thyroidectomy. At operation, MTC was found in seven patients (age 6–56 years), CCH in six patients (age 13–40 years) and normal thyroid histology was present in a single patient (age 27 years). One of the seven patients with MTC died from widespread metastases at age 12 years. Nine of the 23 gene carriers delayed operative intervention. Four of the nine patients have undergone biochemical testing. Three of the four patients have a raised calcitonin level and a single patient remains clinically and biochemically negative at age 40 years.

Conclusion: Penetrance of the c804 mutation is highly variable. In contrast to initial reports, however, MTC associated with sequence abnormalities at this site has aggressive potential. Therefore, prophylactic thyroidectomy remains a reasonable approach in children testing genetically positive.

Phaeochromocytoma: Inherited associations, bilaterality and cortex preservation

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Background: Hereditary phaeochromocytoma (HP) is characterized by early onset, bilateral adrenal involvement, low malignancy rate and genetic linkage with certain familial syndromes. This retrospective review was intended to show the high yield of surveillance, predictable bilaterality and the challenge of cortex-sparing adrenalectomy.

Methods: From 1964 to 1999, 32 patients with HP (mean age 29 years) were treated at a single institution and followed for a mean of 7 (range 0.5–24) years. There were 15 patients with multiple endocrine neoplasia type 2A (MEN2A), 12 with

von Hippel-Lindau disease (VHL), three with von Recklinghausen's disease (VRD) and two patients with familial pheochromocytoma (FP). Twenty-six of 32 patients underwent bilateral adrenalectomy (12 metachronous). Subtotal resection with orthotopic cortex preservation was performed in four patients and heterotopic autografting in 14 patients. Subcapsular segments were harvested and implanted into the rectus muscle after histological confirmation of the absence of medullary tissue. The following variables were assessed: presenting signs, interval of metachronous disease, recurrence, outcome of cortex preservation and survival.

Results: Pheochromocytoma was the first manifestation in six of 12 patients with VHL and four of 15 with MEN2A. Surveillance uncovered medullary thyroid cancer in five of 15 patients with MEN2A, and haemangioblastomas, renal cell carcinoma and islet cell tumours in seven of 15 patients with VHL and VRD. HP was bilateral in 26 of 32 cases (14 of 15 MEN2A, eight of 12 VHL, two of three VRD and both FP). In 12 cases of metachronous HP, the mean interval between adrenalectomy was 67 (range 9–156) months. Three of four patients who underwent orthotopic preservation of the adrenal cortex developed recurrence compared with none of 14 patients with heterotopic autotransplantation of cortical tissue. Four patients in this latter group had normal serum cortisol levels and required no exogenous replacement therapy. There was one case of malignant HP and there was no surgical death.

Conclusion: Inherited bilateral pheochromocytoma is derived from medullary hyperplasia. The long interval of metachronous pheochromocytoma argues against prophylactic removal of the contralateral 'normal' adrenal gland. Pheochromocytoma frequently heralds coexisting silent VHL or MEN-2, mandating surveillance for inherited associations. Total adrenalectomy and heterotopic autotransplantation of medulla-free cortex may diminish the need for lifelong steroid substitution and eliminates recurrence.

Normal preoperative levels of parathyroid hormone signify a mild form of primary hyperparathyroidism

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Background: Primary hyperparathyroidism (pHPT) is characterized by an inappropriate serum level of parathyroid hormone (PTH) in relation to the serum level of calcium. Nowadays, patients often are diagnosed with an overtly asymptomatic pHPT with mild or even intermittent hypercalcaemia. Indeed, health screening surveys have shown that a significant proportion of patients with pHPT is normocalcaemic. Most studies also demonstrate patients with PTH levels in the upper normal range. The aim of the present study was to

define subgroups of patients with mild pHPT, which potentially could give valuable insights into the pathogenesis of the disease.

Methods: Two hundred and seven consecutive patients, 157 women and 50 men, operated for pHPT were investigated with biochemical variables known to reflect PTH activity and calcium metabolism, and bone mineral content. The pre-operative diagnosis of pHPT was based on the presence of hypercalcaemia combined with an inappropriate serum concentration of PTH. Thus, no patient was persistently normocalcaemic. Mean(s.d.) age of the patients was 64(14) years and mean(s.d.) serum level of calcium was 2.78(0.19) mmol l⁻¹. On the basis of serum levels of PTH and calcium the day before surgery, patients were divided into subgroups.

Results: One hundred and sixty-two patients (78 per cent) had raised levels of PTH and calcium the day before surgery (group 1), 25 patients (12 per cent) had a raised level of PTH and normal level of calcium (intermittent normocalcaemia) (group 2) and 20 patients (10 per cent) had a normal PTH level and raised calcium level (group 3). Between-group analyses demonstrated differences between groups in age, bone density, renal function and adenoma weight, and serum levels of alkaline phosphate, osteocalcin and urate. Except for lower adenoma weights, patients in group 2 did not essentially differ from those in group 1. However, patients in group 3 were younger, had better renal function, lower biochemical bone turnover and higher bone mineral content than patients in the other two groups.

Conclusion: These data support the existence of subgroups of mild pHPT. Patients with a serum level of PTH within the normal range were characterized by less biochemical derangement and better bone mineral content. This finding suggests that PTH rather than calcium reflects the severity of the disease.

Cardiac dysfunction during exercise in patients with primary hyperparathyroidism

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Background: 'Non-traditional' manifestations of primary hyperparathyroidism (HPT) are controversial, and include morbidity, mortality and risk factors for cardiovascular diseases with some prospects of normalization by parathyroidectomy (PTX). This study evaluated previously unexplored data on cardiac function during exercise in HPT.

Methods: Thirty patients with HPT (mean(s.d.) serum calcium 2.96(0.24) mmol l⁻¹) and 30 normocalcaemic controls (selected randomly from the background population, and matched for age and sex) underwent exercise testing, echocardiography and

24-h ambulatory blood pressure recordings before and a mean of 13 months after PTX.

Results: HPT was associated with higher systolic blood pressure during exercise (mean(s.d.) 223(28) *versus* 203(33) mmHg; $P=0.02$), which correlated to the left ventricular (LV) mass and serum PTH ($P=0.014$, $P=0.004$); higher LV mass in men (mean(s.d.) 142(20) *versus* 113(28) g m⁻²), which might relate to the hypertrophic effect of PTH; and increased LV isovolumic relaxation times (mean(s.d.) 102(19) *versus* 91(15) ms; $P=0.018$), indicating LV diastolic dysfunction. ST depression during exercise decreased significantly (mean(s.d.) -1.0(0.9) *versus* 0.7(0.5) mm; $P=0.028$) and LV mass declined in proportion with the time after PTX ($P=0.04$ in men). PTX also affected systolic functions, as fractional shortening, atrioventricular plane displacement and systolic index decreased in men ($P=0.05$, $P=0.04$, $P=0.04$). Twenty-four-hour blood pressures were higher in HPT ($P=0.008$), when subjects on β -blockers (seven patients, five controls) were excluded, and were unaltered by PTX.

Conclusion: LV systolic and diastolic dysfunction occurs in HPT. The diastolic dysfunction seems to diminish with time after PTX, while the positive inotropic effect of calcium in itself may alleviate the systolic dysfunction.

Intraoperative decay profile of intact (1–84) parathyroid hormone in surgery for secondary hyperparathyroidism in a consecutive series of 50 patients on haemodialysis

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Background: The usefulness of rapid intraoperative monitoring of intact (1–84) parathyroid hormone (PTH) is not clearly defined in the surgical management of secondary HPT in the patients on haemodialysis. The aim of this study was to define the normal pattern of decay during surgery for secondary HPT using the rapid intact (1–84) PTH assay during operation.

Methods: Fifty patients on haemodialysis underwent neck exploration for secondary HPT. The therapeutic goal in all patients was the subtotal resection of four or more glands and bilateral transcervical thymectomy. PTH levels were monitored using a rapid immunochemiluminometric assay. Peripheral blood samples were assayed at induction of anaesthesia, after dissection but before resection, and 20 and 40 min after resection in all patients. All patients were followed up for at least 6 months. PTH levels were expressed as absolute values, as multiples of the upper limit of normal and as the percentage decline from pre-excision values.

Results: Forty-eight patients (96 per cent) were considered cured after surgery. Twenty patients (40 per cent) had a PTH

level less than twice normal and 20 patients (40 per cent) had a PTH level between two and four times normal at 20 min. At late follow-up, all these patients were cured. Ten patients (20 per cent) had a PTH level greater than four times normal at 20 min. Eight of these patients were cured. Seven of these eight had a PTH level at 20 min, while not less than four times normal, less than 40 per cent of the original value. In contrast, the two failures had neither a decline to less than four times normal nor a decay to less than 40 per cent of the original value. One has been reoperated with resection of a fifth gland and one awaits reoperation.

Conclusion: The intraoperative decay of PTH during surgery for secondary HPT in patients on haemodialysis is slower than that in patients with normal renal function. However, 20 min after resection, a decline to less than four times the upper limit of normal is predictive of cure. Variability of decay slopes in individual patients may reflect molecular heterogeneity or biphasic metabolism of the hormone.

Pitfalls of Intraoperative (1–84) parathyroid hormone measurement during surgery for primary hyperparathyroidism in 154 consecutive operations

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Background: Rapid intraoperative assay of peripheral blood intact parathyroid hormone (PTH) levels has been proposed to supersede frozen-section analysis and assure complete removal of pathological tissue after unilateral (minimal access) exploration. This is a review of the author's surgical, pathological and rapid PTH assay results.

Methods: Some 152 patients (26 men) had 154 explorations for primary hyperparathyroidism (HPT) with rapid intraoperative assay of intact PTH at Centre Hospitalier Regional et Universitaire de Lille.

Results: After neck dissection, before removal of any tissue, the PTH level altered from 11 to 900 per cent of the level at induction of anaesthesia. Decay of blood PTH levels after excision was rapid but some late raised levels may have been due to a pre-excision increase. Recurrent or persistent HPT was seen in eight patients. This was predicted correctly in two and missed in six by the PTH assay (i.e. PTH greater than 50 per cent at more than 5 min). One Schwannoma and one thyroid nodule were removed resulting in diagnostic drops of PTH. There was no instance of non-hyperparathyroid tissue removal and intraoperative PTH assay. Multiple pathological glands were missed by PTH assay in four patients and predicted in a further two. In five patients the fall in PTH was slow; one was taking lithium, one was in mild renal failure and one had

such a high initial PTH level that the assay saturated and it appeared that the results remained static. In 140 operations HPT was identified correctly and excised with a concomitant drop in PTH.

Conclusion: The intraoperative PTH levels vary markedly in either direction between induction of anaesthesia and the end of dissection. After excision of hyperparathyroid tissue the PTH level normally falls briskly from the postdissection level. The number of patients with a potentially unfavourable outcome is small; these data suggest that rapid intraoperative PTH assay would have missed further HPT in ten of 14 instances had the surgical strategy been solely dependent on PTH levels. The routine use of intraoperative PTH assay in surgery for primary HPT is therefore questioned.

Endoscopic endocrine neck surgery with carbon dioxide insufflation: the effect on intracranial pressure

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Background: The endoscopic approach to the thyroid and parathyroid glands requires insufflation with carbon dioxide at 10–15 mmHg. This may decrease the cerebral venous return and increase intracranial pressure (ICP). The aim of this study was to evaluate the effect of carbon dioxide neck insufflation on ICP and haemodynamic variables.

Methods: Twelve 25-kg pigs underwent endoscopic thyroid dissection using carbon dioxide insufflation at 0 mmHg (sham), 10 mmHg (G10), 15 mmHg (G15) and 20 mmHg (G20). Three pigs were used in each group. ICP, mean arterial pressure, central venous blood pressure (CVP), cardiac output and blood gas were measured at baseline, 30, 60 and 120 min.

Results: There were no differences in mean ICP between the sham group and G10. However, ICP significantly increased in G15 and G20. The partial pressure of carbon dioxide was similar in G10 and G15 (mean(s.d.) 49.8(2.4) and 49.8(5.2) mmHg respectively at 120 min), while it was dramatically increased in G20 (63.1(6.9) mmHg at 120 min). Haemodynamic parameters were stable in all groups except for G20 in which CVP significantly increased with respect to baseline (8.5(2.1) versus 1.3(1.5) mmHg; $P < 0.01$). Jugular vein collapse occurred during endoscopic dissection at all insufflation pressures, but pigs operated at 10 mmHg were able to maintain an intermittent blood flow.

Conclusion: A severe increase in ICP occurs with insufflation pressures higher than 15 mmHg, possibly owing to decreased cervical venous blood flow. Carbon dioxide insufflation up to 10 mmHg does not alter ICP, and is recommended for clinical application in endoscopic endocrine neck surgery.

Discovery of germline and somatic mutations in apparently sporadic parathyroid tumours

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Background: To discriminate between sporadic and hereditary parathyroid tumours and characterize multiple endocrine neoplasia type 1 (*MEN1*) somatic mutations, *MEN1* gene mutations were examined in patients with apparently sporadic parathyroid tumours.

Methods: DNA was extracted from fresh frozen parathyroid tumour specimens from 112 patients, as well as from peripheral blood leucocytes (PBL) from 60 of the 112 patients. Sequencing was performed to examine exons 2–10 of the *MEN1* gene for mutations. In addition, exons 10 and 11 of the *RET* gene were sequenced.

Results: *MEN1* mutations were found in 25 (22 per cent) of the 112 patients. Two patients had two simultaneous point-mutations. A total of 27 mutations were characterized, 24 of which have not been reported previously. There were seven nonsense mutations, ten frameshift mutations, two splice-site deletions, five missense mutations and three in-frame mutations. Nineteen mutations resulted in truncation of menin protein. Germline *MEN1* mutations were found in three of 60 patients who had no family history of endocrine tumours associated with *MEN1*, and these patients were identified as *MEN1* gene family probands. No somatic or germline *RET* exon 10 and 11 mutations were found in this series.

Conclusion: These findings suggest that *MEN1* gene mutation may be associated not only with endocrine tumours of affected patients with *MEN1* but also with sporadic parathyroid tumours. *MEN1* gene analysis can distinguish inheritable from non-inheritable parathyroid tumours and *MEN1* gene evaluation of patients with apparently sporadic parathyroid tumours is necessary before parathyroid surgery.

Evaluation of Wilm's tumour suppressor gene and insulin-like growth factor receptors in parathyroid glands

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Background: The precise cause of hyperparathyroidism (HPT) is uncertain. Alteration of growth factors (epidermal growth factor, fibroblast growth factor) and genetic mutations (parathyroid hormone (*PTH*) gene (11p15), *PRAD1* oncogene (11q13) and multiple endocrine neoplasia type 1 (*MEN1*) gene (11q13)) are implicated in the pathogenesis. The escape of

secretory function from physiological control and excess growth is still incompletely understood. The insulin-like growth factor (IGF) axis is a ubiquitous growth and regulatory system (IGF-1 and -II, IGF receptors (IGFRs) and binding proteins (IGFBPs)). Hormonal/endocrine signals (e.g. androgens, thyroid-stimulating hormone) and tumour suppressor genes (e.g. Wilms' tumour suppressor gene (*WT-1*) (11p13) and *p53*) modulate the IGF axis. Expression of the *WT-1* gene is tissue specific (kidney, mesothelium, prostate). Wild-type *WT-1* governs normal kidney development and mutation results in Wilm's tumour. Loss of transcriptional repression of *WT-1* and IGF control can lead to mitogenesis. A mutation (chromosome 11) appears to be the key event in the evolution of primary HPT. This mutation may increase IGFR expression, IGF production giving rise to unregulated autocrine growth. In polyclonal hyperplasia (secondary HPT and MEN1) a serum factor initiates polyclonal growth, thereby increasing the susceptibility to mutation and resulting in nodular hyperplasia.

Methods: Immunohistochemical examination of paraffin-embedded parathyroid glands was done using polyclonal anti-*WT-1* (C19, Santa Cruz) and anti-IGFR-I (C20, Santa Cruz) antibodies and a horseradish peroxidase-labelled secondary antibody for detection. The strength of immunoreactivity was graded using a standardized colour chart and assessed independently by three observers.

Results: Two hundred and fifty-four parathyroid glands from 112 patients were examined. There were 81 women and 31 men (2.6:1). Of these, 94 had primary HPT (70 women) and 18 secondary HPT (11 women). Immunoreactivity to *WT-1* was found in normal parathyroid glands. In contrast, reduced *WT-1* immunostaining was observed in abnormal parathyroid glands. Positive immunostaining for IGFR-I was found in all parathyroid glands. Increased immunoreactivity was found in pathological compared with normal glands.

Conclusion: *WT-1* and IGFR are expressed in parathyroid cells. Abnormal expression of *WT-1* and the IGF axis may play a role in the pathogenesis of HPT.

Non-invasive imaging of freshly excised parathyroid glands using confocal reflectance microscopy

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Background: Successful surgical management of primary hyperparathyroidism requires an understanding of the underlying pathological diagnosis. Various methods have been employed to distinguish normal from hyperfunctional diseased glands. Confocal reflectance microscopy (CRM) is a novel optical method of imaging tissue non-invasively without the need for fixation, sectioning and staining as in standard histopathology. Gray-scale images are displayed in real time

on a monitor, and represent horizontal (*en face*) optical sections through the tissue. Using CRM, the goal of this study was to delineate histological features characteristic of the parathyroid gland, and to determine if confocal imaging could distinguish normal from adenomatous parathyroid tissue.

Methods: In this pilot observational cohort study, a total of 18 parathyroid glands was imaged using CRM immediately after excision in eight patients undergoing surgery for primary hyperparathyroidism. Confocal images were compared with corresponding permanent, haematoxylin and eosin-stained sections obtained from the same gland. For each patient, the percentage area occupied by fat cells was calculated in ten independent images ($593\ \mu\text{m} \times 509\ \mu\text{m}$) of both normal and diseased glands.

Results: Characteristic histological features of the parathyroid gland were readily discernible by CRM and correlated well with permanent, haematoxylin and eosin-stained sections. The fat content of both normal and diseased glands could be determined easily. The percentage area occupied by fat cells was distinctly different in normal (mean(s.d.) 21.8(5.3) per cent) and diseased (0.9(2.4) per cent) parathyroid glands.

Conclusion: CRM rapidly revealed histological features of the parathyroid gland without histological processing. This new, simple, rapid and non-invasive technique has the potential for use as an adjunct to frozen-section analysis in intraoperative consultation during parathyroidectomy. This may provide a technique for *in situ* histological diagnosis of endocrine or other tissues without an excisional biopsy. Work is currently under way to develop an intraoperative probe for *in vivo* use.

Risk profile for bone fractures in primary hyperparathyroidism

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Background: Contemporary patients with primary hyperparathyroidism (pHPT) have an increased fracture risk, although they are often otherwise asymptomatic with mild hypercalcaemia. Decreased bone density has, therefore, been considered an indication for surgery. However, many patients with pHPT are old with concomitant chronic diseases and therefore have a multifocal risk profile for osteoporosis and bone fractures. The aim of the present study was to evaluate bone density as well as other clinical and biochemical variables of importance for bone metabolism with regard to fracture risk in patients with pHPT.

Methods: Two hundred and five consecutive patients, 154 women and 51 men, operated for pHPT were investigated for bone mineral content (BMC), biochemical variables reflecting bone metabolism and severity of pHPT, medication and

potential other risk factors for osteoporosis. Mean(s.d.) age of the patients was 64(14) years and serum level of calcium was 2.78(0.18) mmol l⁻¹.

Results: Eighteen patients (9 per cent) had a history of at least one bone fracture during the 5 years before pHPT surgery. In univariate analyses age, BMC, serum level of PTH, 25-hydroxyvitamin D, alkaline phosphatase and collagen telopeptide (ICTP), cortisone treatment and a history of cardiovascular disease were found to be associated with a history of bone fractures. When these variables, and in addition sex, were included in a multiple logistic regression analysis, ICTP was the only variable independently related to bone fractures.

Conclusion: The present data highlight the multifocal bone fracture risk profile in pHPT including low bone density. However, bone resorption (ICTP) was the only variable in the multivariate analysis that was independently associated with bone fractures in pHPT. This finding supports the important role of bone resorption in the pathogenesis of fractures in pHPT. Furthermore, it suggests that ICTP may be a useful tool for risk evaluation of fractures in patients with pHPT.

Overexpression of haem oxygenase 1 protects allogeneic thyroid grafts from rejection in naive mice

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Background: Endocrine allografts are an option for the treatment of endocrine failure. This study examined whether anti-CD4 monoclonal antibody (mAb) could induce survival of allogeneic thyroid grafts and investigated the mechanisms involved in graft survival.

Methods and Results: One lobe of thyroid was transplanted under the kidney capsule and graft survival was examined histologically. C57BL/10 (H2b) thyroids were rejected in naive CBA (H2k) mice within 14 days after transplantation. When mice were treated with a depleting anti-CD4 mAb (YTA 3-1; 100 µg on day -1, 0 and 3), all C57BL/10 thyroid grafts survived for over 30 days. In order to determine if donor-specific tolerance had been induced, mice with the surviving C57BL/10 thyroid grafts were transplanted with second C57BL/10 or Balb/c (H2d) thyroids under the left kidney capsule at 30 days. Interestingly, all of the second grafts were rejected in the left kidney capsule but the first C57BL/10 thyroid grafts continued to survive in the right kidney capsule for a further 30 days. These findings suggest that grafts themselves were modified under anti-CD4 mAb treatment. To confirm this hypothesis, C57BL/10 thyroid grafts in mice

treated with anti-CD4 mAb were resected and retransplanted into naive mice 30 days after transplantation. All of the grafts survived when retransplanted to naive mice and this was found to correlate with overexpression of haem oxygenase 1 in the thyroid grafts. In an attempt to demonstrate the pivotal role of haem oxygenase 1 on graft survival, an inhibitor of haem oxygenase 1 (zinc protoporphyrin) or control compound (copper protoporphyrin) that did not inhibit the enzyme was injected intraperitoneally (30 mmol l⁻¹ every day) after transplantation of C57BL/10 thyroid grafts into the primary CBA recipients treated with anti-CD4 mAb. The grafts in mice treated with zinc protoporphyrin but not copper protoporphyrin were rejected when retransplanted to naive recipients.

Conclusion: Overexpression of haem oxygenase 1 protects allogeneic thyroid grafts from rejection in recipients treated with anti-CD4 mAb. This observation may be applied for clinical endocrine grafts using gene transfer of haem oxygenase 1.

Murine model of allogeneic adrenocortical cell transplantation: perspectives for the treatment of Addison's disease in man

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Background: Hormone substitution for the treatment of adrenocortical insufficiency (Addison's disease) does not adequately substitute the physiological circadian secretion of corticosteroids leading to long-term sequelae and reduced quality of life. Moreover, oral administration of corticosteroids cannot mimic the hormone peaks required in stress situations. This lack of adaptation to physical and psychological stress may lead to life-threatening Addisonian crises. Allogeneic transplantation of adrenal cortex may offer an alternative.

Methods: Major histocompatibility complex (MHC) class I transgenic mice (H-2Kb) were used for the implementation of an animal model of adrenocortical transplantation. Tissue fragments or selectively isolated cell suspensions of the adrenal cortex were transplanted underneath the kidney capsule of adrenalectomized mice. Kb-transgenic murine cells as well as allogeneic adrenal cortex cells were cocultured in mixed lymphocyte cultures (MLC) in order to examine the allo-immune response. Lymphocytes from T-cell receptor transgenic mice and normal allogeneic mice respectively served as responder cells. The immune response, i.e. lymphocyte proliferation, was quantified by measuring the [³H]thymidine uptake of responder cells. The effect of corticosteroids secreted by adrenocortical cells was antagonized by the steroid receptor antagonist Mifepristone (RU 486).

Results: Without need for immunosuppressive drugs, adrenocortical grafts were demonstrated to proliferate and produce corticosteroids at physiological concentrations 20 days after transplantation. Coculture of adrenal cortical cells in MLC markedly suppressed lymphocyte proliferation. This inhibited immune response was not completely antagonized by RU 486.

Conclusion: *In vitro*, the presence of adrenocortical cells potently suppressed allogeneic immune responses. This effect was not only due to the secretion of corticosteroids, pointing to a additional immunomodulatory property of adrenocortical cells. Successful allogeneic transplantation of MHC-II-matched adrenal cortex grafts in a murine model raises the possibility of applying these methods in humans.

Management of incidentally discovered adrenal masses and risk of malignancy

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Background: Incidentally discovered adrenal masses larger than 1 cm are relatively frequent, but the correct management of such lesions is not well established.

Methods: Between 1980 and 1999, 158 patients (73 men (46 per cent) and 85 women (54 per cent), of median age 53 years) with adrenal incidentalomas larger than 2 cm were observed. Sixty-eight patients (43 per cent) underwent adrenalectomy. The reasons for surgery were: (1) suspicious appearance on computed tomography (CT) or magnetic resonance imaging (MRI) or no uptake at 75-selenium-norcholesterol scintigraphy (NCS) ($n=22$), (2) increase in size of more than 1 cm ($n=15$), (3) subclinical endocrine hyperfunction ($n=14$), (4) size greater than 5 cm ($n=12$) and (5) suspicious imaging-guided fine-needle aspiration cytology (FNAC) ($n=5$).

Results: Pathological examination showed 39 adrenocortical adenomas (57 per cent), 20 adrenal malignancies (29 per cent) (15 carcinomas, three unsuspected metastases and two non-functioning malignant pheochromocytomas) and nine various benign lesions (13 per cent). All masses increased in size were benign. Seven malignant tumours were 3–4 cm and 14 benign lesions were 5–6 cm in size. Sensitivity and specificity in detection of malignancy were 100 and 100 per cent for NCS ($n=34$) and FNAC ($n=9$), 75 and 94 per cent for CT ($n=68$), and 88 and 100 per cent for MRI ($n=26$) respectively.

Conclusion: To differentiate benign and malignant incidentalomas NCS and FNAC are more sensitive than CT and MRI, while the size criteria are of little value.

Limitations of size as a criterion in evaluating adrenal tumours

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Background: Size is considered the single best predictor of malignancy in evaluating adrenal neoplasms identified incidentally during abdominal imaging, yet small adrenal cortical cancers have been reported previously from several centres.

Methods: This was a retrospective evaluation of the value of tumour size and other preoperative clinical parameters in predicting the presence or absence of malignancy in adult patients who underwent adrenalectomy for an adrenal tumour at this institution.

Results: One hundred and sixteen patients underwent adrenalectomy. Diagnoses were adrenal cortical carcinoma ($n=38$), pheochromocytoma ($n=27$), metastasis to the adrenal gland ($n=11$) and benign tumours ($n=40$) (cortical adenoma, 23; cyst, two; cortical hyperplasia, five; ganglioneuroma, four; myelolipoma, six). The median size of the adrenal cortical carcinomas was 9.2 (range 1.7–30) cm; five tumours were smaller than 5.0 cm. The median overall size of the benign tumours (excluding pheochromocytomas) was 4.0 cm; the median size of the adrenal cortical adenomas was 3.0 cm. Eleven benign tumours were larger than 5.0 cm, including two cortical adenomas. The radiographic features of three of five small adrenal cancers correctly predicted malignancy; the remaining two patients with small cancers had symptoms related to functioning tumours. Conversely, the radiographic features of seven of 11 large benign adrenal tumours correctly predicted benign histology, including five of five myelolipomas.

Conclusion: While size remains a good predictor of histology and clinical behaviour of functioning and non-functioning adrenal neoplasms, both small adrenal cortical cancers and large benign tumours occur with measurable frequency. High-quality imaging studies (computed tomography and magnetic resonance imaging) may be helpful in identifying relatively small yet radiographically atypical adrenal tumours more likely to be cancers, as well as radiographically characteristic benign myelolipomas which may be followed selectively.

Laparoscopic adrenalectomy for malignancy

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Background: Controversy exists as to whether laparoscopic adrenalectomy should be performed for malignant or potentially malignant tumours affecting the adrenals.

Methods: This was a retrospective analysis of all patients undergoing laparoscopic adrenalectomy at this institution from 1993 to 1999. Patients were classified by their preoperative diagnosis and analysed with respect to their final pathological diagnosis, operation and postoperative course.

Results: Some 121 patients underwent 133 laparoscopic adrenalectomies. Preoperative classification was type I (benign disease; 67 patients), type II (possibly malignant disease; 46 patients) and type III (malignant disease; eight patients). After operation, 11 patients had malignancy on pathological diagnosis including all eight patients with known preoperative malignancy (one adrenocortical carcinoma (3 × 3 cm) presenting as a virilizing tumour, two neuroblastomas, one lymphoma, one bilateral staged adrenalectomy for metastatic colon cancer, two metastatic lung cancers and one metastatic renal cell carcinoma). One patient with adrenocortical cancer (8 × 6 cm) had incorrect preoperative classification by cytology (type I; oncocytoma). Two of 14 patients with Cushing's adrenal tumour (type II) had adrenocortical cancer (12 × 9 cm and 3 × 3 cm). Mean length of stay was 1.8 days in patients with malignancy. No procedure was converted to open adrenalectomy and no significant complications were encountered. Only the four patients with adrenocortical carcinoma had a recurrence (two required open re-resection 3 months and 2 years after initial operation, one had laparoscopic re-resection 2 years after operation for local recurrence and one presented with recurrence 1 year after operation).

Conclusion: Forty-five per cent of patients undergoing laparoscopic adrenalectomy may be classified as having potentially malignant disease (type II or III). Most malignant tumours of the adrenals can be treated laparoscopically, but adrenocortical carcinomas are at high risk of recurrence after laparoscopic adrenalectomy.

Total parathyroidectomy in patients with chronic renal failure

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Background: Total parathyroidectomy without reimplantation has been advocated as a treatment for hyperparathyroidism in patients with end-stage chronic renal failure. However, there are concerns that a lack of endogenous parathyroid hormone (PTH) can result in hypocalcaemia and adynamic bone disease. The aim of this study was to identify whether this is a significant clinical problem.

Methods: A review of 56 (51 four-gland and five three-gland) histologically confirmed parathyroidectomies performed by the same surgeon between 1994 and 1999 was performed. Mean(s.d.) follow-up was 30(22) months.

Results: Patients could be divided into three groups on the basis of a postoperative serum PTH concentration that was either undetectable (less than 0.1 pmol l⁻¹), less than the upper limit of normal (7.6 pmol l⁻¹ or less) or raised (more than

	PTH (pmol l ⁻¹)		
	<0.1 (n=17)	≤7.6 (n=29)	>7.6 (n=10)
Calca (calcitriol) (µg day⁻¹)			
Discharge	8.5(6.7)	9.7(5.8)	7.8(6.3)
Latest	0.8(1.1)	0.4(0.5)	0.5(0.7)
Oral calcium (mg day⁻¹)			
Discharge	700(1250)*	150(200)	360(570)
Latest	1325(1580)	1675(1880)	1690(1650)
Ionized calcium (mmol l⁻¹)			
Preoperative	2.65(0.28)	2.58(0.21)	2.65(0.43)
Latest	2.42(0.22)	2.43(0.22)	2.65(0.61)
Bone pain improved resolved	11 of 17	14 of 29	3 of 10
Alkaline phosphatase (mmol l⁻¹)			
Preoperative	179(115)	201(181)	238(143)
Latest	88(36)	115(84)	127(90)

Values are mean(s.d.). *P < 0.05

7.6 pmol l⁻¹). Demographics, mean number of glands excised and histology were similar in each group. Patients with a raised serum level of PTH had a mean(s.d.) value of 54.1(73.3) pmol l⁻¹. Three-gland parathyroidectomy occurred in three patients, raising the possibility of ectopic glands. Two patients had neck re-exploration after four-gland parathyroidectomy; an adenoma and an ectopic gland were identified. One patient had a parathyroid adenocarcinoma.

Conclusion: Total parathyroidectomy may leave residual functional parathyroid tissue that is not visualized at surgery. However, in patients who had no functional parathyroid tissue after operation there was little clinical or biochemical evidence of an increased incidence of hypocalcaemia or bone disease.

Randomized trial of parathyroidectomy in mild, asymptomatic primary hyperparathyroidism as measured by the SF-36 health survey

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Background: Management of patients with asymptomatic primary hyperparathyroidism (HPT) remains controversial despite a National Institutes of Health consensus statement on this issue. As part of the above statement, a randomized clinical trial was recommended since none exist to address this issue.

Methods: Informed consent was obtained from 53 asymptomatic patients with confirmed primary HPT who agreed to participate in this randomized clinical trial of parathyroidectomy versus observation. Upon entry to the study and 24 months later the patients completed the SF-36 health survey which is an

instrument that measures nine different levels of function. Scores were tabulated and the difference over 24 months between operated and non-operated patients was compared with Student's *t* test.

Results: Fifty-three patients (42 women and 11 men) with asymptomatic, mild primary HPT (serum calcium 10.1–11.5 mg dl⁻¹) who agreed to participate were randomized into either a surgical group or an observation group. Mean serum calcium for these patients was 10.3 mg dl⁻¹. The only demographic difference between the groups was age; the operated group was older (66.7 *versus* 62.6 years; *P* < 0.03). Scores on three of the nine domains (health perception, emotional problems and social functioning) on the SF-36 were significantly different (*P* < 0.05), all favouring the operated group.

Conclusion: Improved function, as measured by the SF-36 health assessment tool, is seen after parathyroidectomy compared with non-operated patients. This work supports surgical management of mild primary HPT at the time of diagnosis since many patients have reversible non-classical symptoms of the disease.

Ultrasonography and sestamibi as the only preoperative imaging tests in reoperation for parathyroid adenoma

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Background: Various non-invasive and invasive tests are used for the localization of parathyroid adenomas in the reoperative setting. To help determine the most efficient algorithm for the evaluation of these patients, use of a combination of ultrasonography and sestamibi as the only preoperative imaging tests was explored.

Methods: This was an analysis of outcomes of 62 consecutive patients (21 men; mean age 55 years) treated between January 1995 and May 1999, and referred for persistent hyperparathyroidism after one (*n* = 47) or more (*n* = 15) previous explorations at which no abnormal parathyroid glands were found. While all patients underwent ultrasonography (all interpreted by one radiologist), computed tomography (CT), magnetic resonance imaging and sestamibi, the success of localization and reoperation was analysed using only the results of ultrasonography and sestamibi. Intraoperative ultrasonography (IOUS) was available in all cases.

Results: Sixty-one patients (98 per cent) had curative reoperations with solitary adenomas confirmed pathologically. One adenoma was not found at operation. Forty-six adenomas (74 per cent) were ectopic including 14 in the tracheo-oesophageal groove and 12 in the anterior mediastinum. The sensitivity, positive predictive value and accuracy for ultrasonography

were 91, 87 and 84 per cent respectively; the corresponding values for sestamibi were 75, 94 and 71 per cent. In 58 (94 per cent) of 62 patients preoperative ultrasonography and/or sestamibi accurately identified the adenoma. In three patients cured by operation, in whom combined ultrasonography and sestamibi was inaccurate, one gland was found by IOUS in strap muscle, one by blind cervical thymectomy and one by sternotomy based on CT findings. Thirty-seven patients (60 per cent) underwent IOUS. In nine of these patients IOUS was essential in guiding resection of the adenomas.

Conclusion: This study supports an algorithm of obtaining ultrasonography and sestamibi as the initial and perhaps only preoperative localization tests for patients with persistent hyperparathyroidism after failed operation at which no abnormal glands were found. Using this algorithm, reoperation should be successful in almost 95 per cent of cases.

Surgical *versus* medical treatment for calciphylaxis

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Background: Calciphylaxis is a rare, painful, life-threatening problem of cutaneous necrosis and refractory healing seen in patients with uraemia and secondary hyperparathyroidism. The pathogenesis involves abnormalities in calcium and phosphorus metabolism, and acute deposition of calcium in tissues.

Methods: The clinical course of 16 patients diagnosed with calciphylaxis at this institution from 1994 to 1998 was reviewed.

Results: Fourteen women and two men, with a mean age of 56 (range 39–70) years, presented with chronic renal disease of various causes, hyperparathyroidism and characteristic skin lesions. All patients underwent intensive medical therapy, including haemodialysis (*n* = 16), parathyroidectomy (PTX) (*n* = 7) and skin debridement of cutaneous lesions (*n* = 8). Mean preoperative serum values in surgical (PTX) *versus* non-surgical patients were: calcium 9.9 and 9.3 mg dl⁻¹ (*P* = 0.25); phosphorus 5.8 and 4.9 mg dl⁻¹ (*P* = 0.04); calcium–phosphorus product 61.6 and 45.2 (*P* = 0.03); and parathyroid hormone (PTH) 56.8 and 5.9 pmol l⁻¹ (*P* = 0.0001) respectively. Mean postoperative values for calcium (8.7 mg dl⁻¹), phosphorus (4.2 mg dl⁻¹), calcium–phosphorus product (30.5) and PTH (4.0 pmol l⁻¹) in surgical patients changed significantly (*P* < 0.05). Median overall survival was 9.4 months with 15 patients now deceased. Median survival was 14.8 and 6.3 months for PTX *versus* no PTX (*P* = 0.22), 14.1 and 6.1 months for skin debridement *versus* no debridement

($P=0.08$), 12.4 and 6.6 months for proximal *versus* distal skin lesions ($P=0.60$), and 6.5 and 13.9 months for diabetic *versus* non-diabetic patients was ($P=0.11$).

Conclusion: Calciphylaxis appears to have a female preponderance with a very dismal prognosis. A multidisciplinary approach using frequent haemodialysis to normalize serum calcium and phosphorus levels, and local debridement of skin lesions seems prudent. PTX cannot be recommended routinely in all such patients unless severe secondary hyperparathyroidism with poorly controlled metabolic disturbance mandates surgery. The exact indications for PTX for calciphylaxis remain unclear.

Normalization of intraoperative parathyroid hormone does not predict normal postoperative parathyroid function

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Background: Intraoperative measurement of intact parathyroid hormone (iPTH) has been used increasingly as a means of confirming complete removal of hyperfunctioning parathyroid tissue. It remains uncertain, however, whether normalization of iPTH levels at operation accurately predicts postoperative values of iPTH.

Methods: Forty-five consecutive patients with primary hyperparathyroidism underwent parathyroidectomy between March and November 1999. Baseline intraoperative iPTH levels were measured before and at manipulation, then subsequently at 5 and 10 min after tissue was removed. Follow-up values were measured at 1- and 3-month intervals.

Results: Before operation the mean(s.d.) iPTH concentration was 211(182) pg mL⁻¹ with a mean serum calcium level of 11.4(1.0) mg dL⁻¹. In all but four patients, the final intraoperative iPTH normalized to absolute values below 60 pg mL⁻¹ (mean 38(36) pg mL⁻¹). One week after operation, serum calcium levels had returned to normal (mean 9.2(0.9) mg dL⁻¹) and this correlated directly with final intraoperative iPTH values when assessed by linear regression analysis ($r=0.373$, $P<0.03$). By 1 month, all but two patients were normocalcaemic (mean 9.6(0.6) mg dL⁻¹) with a mean iPTH of 81(99) pg mL⁻¹. There was no correlation between the final intraoperative iPTH and postoperative iPTH values as determined by linear regression analysis ($r=0.035$, $P<0.881$). Both patients with persistent hypercalcaemia at 1 month had appropriate intraoperative decreases in iPTH level.

Conclusion: Although there is significant correlation between intraoperative iPTH levels and postoperative serum calcium levels, this does not hold true for postoperative iPTH levels. There was a 4 per cent failure rate in correcting postoperative calcium levels and a 20 per cent failure rate in normalizing

postoperative iPTH levels despite appropriate intraoperative decreases in iPTH.

Late parathyroid function following successful parathyroidectomy guided by intraoperative hormone assay compared with standard bilateral neck exploration

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Background: Controversy continues between bilateral neck exploration and limited parathyroidectomy guided by gland hyperfunction. While one approach depends on gland size and histopathology, the other limits excision to hypersecreting glands only. Although both methods claim early operative success, the late recurrence rate with limited exploration is unknown. Late biochemical outcomes from these two operative approaches are reported.

Methods: Some 301 consecutive patients with primary hyperparathyroidism were followed 6–495 months after successful parathyroidectomy; 164 patients had bilateral neck exploration with excision of enlarged glands (group 1) and 137 patients had glands excised based on hypersecretion (group 2). Calcium and intact parathyroid hormone (iPTH) levels were measured yearly. Recurrent parathyroid gland hypersecretion was determined by iPTH levels above the normal range.

Results: In group 1, a single gland was excised in 150 patients (91 per cent); 15 (9 per cent) of 164 had late raised iPTH levels (12 normocalcaemic). In group 2, 133 patients (97 per cent) had a single gland excised and 21 (15 per cent) of 137 had high iPTH levels (19 normocalcaemic). The number of patients with more than one gland excised in group 1 (9 per cent) was three times higher than that in group 2 (3 per cent) ($P<0.04$). There was no statistical difference in the incidence of recurrent hyperfunctioning glands between the two operative approaches (χ^2 test).

Conclusion: Based on late parathyroid gland function, parathyroidectomy guided by gland hyperfunction yielded comparable results to bilateral neck exploration. Multiple gland excision based on gross appearance alone may result in unnecessary excision of normal glands and possible hypoparathyroidism.

Cardiac disease and midgut carcinoid syndrome

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Background: Valvular heart disease is a well known complication of the midgut carcinoid syndrome but its impact on

survival and effects of modern tumour treatment remain to be analysed.

Methods: In a prospective study cardiac abnormalities and clinical outcome were analysed in 64 consecutive patients with high urinary excretion of the serotonin metabolite 5-HIAA and carcinoid tumours with liver metastases (mean(s.d.) follow-up 119(7) months). A tumour reduction programme by radical surgery alone (including hemihepatectomy) or with hepatic artery embolization following primary surgery (in bilobar liver disease) was offered to all patients. At entry into the study, patients underwent Doppler echocardiography, exercise electrocardiography, Holter monitoring and urinary 5-HIAA determination.

Results: At follow-up, patients were grouped according to clinical outcome. Twenty-four patients were alive, 11 after radical surgery alone (group 1) and 13 after embolization plus octreotide (group 2). Forty patients had died during follow-up (group 3), three with radical surgery (unrelated disease) and 27 patients with embolization plus octreotide. Ten deceased patients had medical therapy alone after primary surgery owing to complicating diseases. The mean 5-HIAA levels before treatment were lower in group 1 (185 mol per 24 h) than in group 2 (956 (mol per 24 h) or group 3 (566 (mol per 24 h). Tricuspid valve structural abnormalities (TSA) were found in 13, 38 and 33 per cent, and holosystolic tricuspid regurgitation (TR) in 36, 54 and 60 per cent of patients in groups 1, 2 and 3 respectively. No patient had pulmonary stenosis, but 9 per cent (group 1), 15 per cent (group 2) and 13 per cent (group 3) had holodiastolic pulmonary regurgitation. A novel index (TSA-TR) of TSA (0-4) and TR (0-4) was formed. Patients with TSA-TR (3 had significantly ($P=0.025$) higher 5-HIAA levels than patients with an index (1. Patients with 5-HIAA levels above 500 (mol per 24 h) demonstrated a significantly ($P=0.04$) higher late-to-early peak ratio (A/E) of diastolic tricuspid Doppler flow than patients with 5-HIAA levels less than 500 (mol per 24 h). Of the six patients who suffered cardiac death, five died from ischaemic heart disease or sudden death and one from advanced right heart failure.

Conclusion: Tricuspid abnormalities were common findings in patients with the midgut carcinoid syndrome and severe findings were related to high urinary excretion of 5-HIAA. The highest initial hormone levels were seen in one of the surviving groups. Sudden or ischaemic heart death was more common than death from right-sided heart failure.

Clinical and genetic analysis of patients with pancreatic neuroendocrine tumours associated with von Hippel-Lindau disease

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Background: Patients with von Hippel-Lindau disease (VHL) are at risk of developing pancreatic cysts, microcystic adenomas and neuroendocrine tumours. Pancreatic neuroendocrine tumours (PNETs) are found in 19 per cent of families with VHL. These tumours can behave in a malignant fashion, with up to 17 per cent of patients developing distant disease. The authors' initial experience with the diagnosis and management of these lesions, with resection based on size greater than 3 cm in imaging studies, has been reported previously. This is a report on their prospective experience using these criteria as well as on the role of genotype/phenotype analysis of germline VHL gene mutations in predicting clinical course.

Methods: Some 389 patients with VHL were screened between December 1998 and December 1999. The diagnosis of PNET was made by either pathological analysis of tissues or by characteristic radiographic appearance on computed tomography and magnetic resonance imaging. VHL gene germline mutations were determined by quantitative Southern blotting to detect deletions of the gene, Southern blotting to detect gene rearrangements, fluorescence *in situ* hybridization to confirm deletions and complete gene sequencing.

Results: Forty-four patients with PNET have been identified. Of these, 25 have undergone definitive surgical resection, five were found to have metastatic disease and 14 are being followed prospectively. No patient who has undergone resection based on the aforementioned tumour size criteria has developed metastatic disease. These patients represent 36 families (19 per cent) of a total of 188 VHL families who have had germline mutation analysis. Compared with all 188 VHL families, those with PNETs are more likely to have missense mutations (58 per cent) and more likely to have intragenic mutations. Four of five patients with metastatic disease have mutations in exon 3 compared with 18 of 39 patients without metastatic disease.

Conclusion: An aggressive approach to imaging for detection and surgical resection based on established size criteria has resulted in the successful management of patients with VHL and PNETs. Analysis of germline mutations may help predict those patients with VHL who are at risk of developing a PNET and which patients with a PNET may benefit from earlier surgical intervention to prevent spread of disease.

Non-insulinoma pancreatogenous hypoglycaemia syndrome

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Background: The authors have reported a newly recognized hypoglycemic disorder, non-insulinoma pancreatogenous

hypoglycaemia syndrome (NIPHS), which is characterized by postprandial hyperinsulinaemic hypoglycaemia, negative 72-h fast, negative transabdominal and intraoperative ultrasonography, spiral computed tomography and coeliac axis angiography, positive selective arterial calcium stimulation test (SACST), absence of insulinoma but presence of islet hypertrophy and nesidioblastosis, and relief of symptoms from gradient-guided partial pancreatectomy. Experience with the next five patients with this disorder (6–10; 1998–1999) compared with the original five (1–5; 1996–1998) is reported.

Results:

Patient	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	F	M	M	F	M	F
Age (years)	37	16	72	72	78	64	29	43	28	28
Symptoms	pc	pc	pc	pc	pc	pc	pc	pc	pc	pc
SACST positive in										
SPA	+	+	+	+		+	+	+	+	
GDA	+		+	+		+		+		
SMA	+				+					+
Surgical resection in relation to SMV	R	L	R	R	L	R	L	R	L	R

*Superior mesenteric artery (SMA) supplied the whole pancreas. SPA, splenic artery; GDA, gastroduodenal artery; SMV, superior mesenteric vein; pc, postprandial hyperinsulinaemic hypoglycaemia; R, right of; L, left of

Wide age range, male predominance, postprandial occurrence of symptoms, negative radiological localization, nesidioblastosis/islet hypertrophy, but no insulinoma characterized all ten cases. Response to SACST indicated widespread islet hyperfunction in patients 1 and 5; limitation to distribution of the SPA and GDA in patients 3, 4, 6 and 8, to distribution of the SPA in patients 2, 7 and 9, and to distribution of the SMA in patient 10. Except for patient 5, pancreatic resection to the left of the SMV was performed when only the SPA was positive on the SACST. Patients 5 and 8 have had recurrence of symptoms; they resolved within 3 months for patient 5.

Conclusion: NIPHS can usually be treated successfully with gradient-guided partial pancreatectomy.

Value of intra-arterial calcium-stimulated venous sampling for regionalization of pancreatic insulinomas

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Background: Although the need for routine preoperative localization of insulinoma is challenged, accurate preoperative

localization is regarded as the prerequisite for successful laparoscopic resection of insulinoma. Intra-arterial calcium stimulation with hepatic venous sampling for insulin gradients (ASVS) has been reported to be the most sensitive preoperative localization technique. The authors' experience with ASVS to localize and guide management of insulinomas is reviewed.

Methods: Between 1991 and 1999, 20 patients underwent surgical resection for insulinomas. Sixteen patients (11 men, five women; median age 43 years) underwent ASVS for preoperative localization of insulinoma based on equivocal standard imaging studies. Intraoperative ultrasonography was performed routinely. The accuracy of ASVS was compared with that of intraoperative findings and other methods of localization.

Results: There was no complication arising from the procedure. A median step-up of tenfold (right 3–37-fold; left 3–72-fold) in insulin level 30–60 s after injection to at least one feeding artery was observed in 14 patients. Enucleation and distal resection were performed in six and ten patients respectively. In the era of laparoscopy, open enucleation and laparoscopic resection were adopted for two tumours each located at the pancreatic head and tail respectively. Twelve of the 14 solitary tumours were located correctly; all four at the head, one of three in the body and all seven at the tail. Two patients with multiple endocrine neoplasia type 1 and multiple tumours had the dominant tumours located at the tail. The overall accuracy of this test was 88 per cent compared with 11, 31, 43 and 67 per cent for ultrasonography, computed tomography, magnetic resonance imaging and endoscopic ultrasonography respectively. Intraoperative ultrasonography readily located two tumours missed by ASVS which, in turn, guided the removal of a tumour located at the splenic hilum that eluded detection by intraoperative ultrasonography.

Conclusion: ASVS is the most accurate preoperative localization tool for localizing insulinomas. It guides the adoption of the minimally invasive approach and, in combination with intraoperative ultrasonography, enhances surgical success in the management of insulinoma.

Neutralizing vascular endothelial growth factor activity inhibits thyroid cancer growth *in vivo*

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Background: Without angiogenesis, tumours cannot grow larger than a few millimetres in size, the limit of diffusion. Vascular endothelial growth factor (VEGF) is an endothelial-specific mitogen and is a major regulator of physiological and pathological angiogenesis. Higher levels of VEGF messenger

RNA expression and VEGF production and secretion have been found in FTC-133 cells than normal thyroid cells.

Methods: To investigate the relationship between VEGF and thyroid tumour angiogenesis and growth, human dermal matrix inoculated with FTC-133 cells was xenografted into nude mice or directly injected subcutaneously. To block the function of VEGF, the neutralizing anti-VEGF monoclonal antibody A.4.6.1 (mAb A.4.6.1) was injected intraperitoneally 100 µg per 0.2 ml twice weekly. As control, an antibody of the same isotype (immunoglobulin G₁), directed against the gp120 protein (Ab 5B6), or phosphate-buffered saline (PBS) was used. To evaluate the dermal matrix as a model for angiogenesis studies, rhVEGF was inoculated into the dermal matrix pocket and xenografted into mice.

Results: *In vivo* study using the dermal matrix showed that the number of blood vessel ingrowths paralleled the concentration of rhVEGF and was highest at the concentration of 100 ng ml⁻¹. Mice treated with the mAb A.4.6.1 developed fewer blood vessels (mean 7 per high-power field (HPF)) than control mice (18 per HPF in Ab 5B6 and 22 per HPF in PBS) ($P < 0.01$). The size of tumours between mAb A.4.6.1- and Ab 5B6- or PBS-treated groups showed a significant difference from the second week after the inoculation of FTC-133 cells. The tumours from mice treated with mAb A.4.6.1 were smaller (mean(s.d.) 0.09(0.02) g at 5 weeks) than tumours from mice treated with Ab 5B6 (5.38(1.15) g) or PBS (4.00(0.72) g) ($P < 0.001$, two-tailed unpaired *t* test).

Conclusion: VEGF is produced by thyroid cancer cell line FTC-133 and stimulates angiogenesis and growth of thyroid cancer. More importantly, this stimulation can be blocked by mAb A.4.6.1.

Outcome of a conservative surgical policy for differentiated thyroid cancer: a prospective population-based cohort study

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Background: The extent of surgery and the requirement for routine total thyroidectomy in patients with papillary or follicular differentiated thyroid cancer (DTC) is contentious. It is desirable to strike a balance between achieving cure and local disease control and avoidable surgical morbidity. Routine total thyroidectomy increases the rate of permanent hypoparathyroidism and may not improve cure or local recurrence rates in patients categorized at low risk. An ongoing prospective study of the outcome of a conservative surgical policy based on an unselected population from the north east of Scotland is reported.

Methods: With few exceptions, all patients with thyroid cancer in north-east Scotland are treated in a specialist unit. Data are recorded prospectively and all patients are reviewed at a

dedicated thyroid clinic or by postal review if they leave the area. The mortality, morbidity (including recurrent laryngeal nerve and parathyroid function), recurrence and reoperation rates, and administration of radioactive iodine are recorded. The population of this region is very stable and follow-up is complete in over 97 per cent of patients. The surgical policy is to remove all macroscopic disease from the neck at the first operation and reserve total thyroidectomy for patients with bilateral disease or who are considered at high risk and likely to require postoperative radioactive iodine therapy.

Results: During the period 1977–1996, 238 patients with thyroid cancer were treated of whom 193 (81 per cent) had DTC. Some 148 (77 per cent) of the DTCs were categorized 'low risk'. Fifty-five (28 per cent) of the 193 patients underwent total or near-total thyroidectomy. The majority of patients (75 per cent low risk; 59 per cent high risk) underwent lobectomy. Seven patients (five low risk; two high risk) have required subsequent completion total thyroidectomy, usually for a rising thyroglobulin level, only three of whom had evidence of DTC in the resected lobe. The mortality rate from DTC was 13 and 1 per cent in high- and low-risk patients respectively. Four (2 per cent) of the 193 patients developed postoperative hypoparathyroidism.

Conclusion: This prospective study suggests that appropriate selection of patients for total thyroidectomy in an endocrine surgical unit is associated with a low mortality rate and little requirement for completion total thyroidectomy. Routine total thyroidectomy is not necessary.

Thyroid surgery with Intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective multicentre study in Germany with 7617 patients

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Background: Injury to the recurrent laryngeal nerve (RLN) is a frequently noted and serious complication in thyroid surgery. Several studies have established that identification of the RLN may reduce the incidence of RLN palsy. To date, no prospective study has evaluated whether the RLN palsy rate can be further reduced by intraoperative neuromonitoring of the RLN.

Methods: Between 1 January and 31 December 1998, surgery for benign and malignant goitre was performed on 7607 patients in 45 hospitals. Data were collected prospectively by questionnaire. RLN function was evaluated before and after operation in all patients. RLN palsy was defined as permanent when there was no evidence of recovery within 6 months after surgery. The RLN palsy rate was adjusted to nerves at risk in the three groups 'no identification of the RLN', 'intraoperative identification of the RLN without neuromonitoring' and

'identification of the RLN with neuromonitoring'. Statistical analysis was by χ^2 test.

Results: Mean patient age was 51.8 years; 72.7 per cent were women. Some 7256 patients were treated for benign goitre (multinodular goitre 74.0 per cent, uninodular goitre 16.6 per cent, recurrent goitre 6.1 per cent, Graves' disease 3.3 per cent, Hashimoto and De Quervain thyroiditis less than 0.1 per cent) and 351 patients for thyroid carcinoma, with a negative selection of recurrent goitre and thyroid carcinoma for the two groups with intraoperative RLN identification ($P < 0.0001$). With respect to the extent of resection, in cases of lobectomy the rate of permanent RLN palsy was 1.5 per cent with intraoperative neuromonitoring which was significantly lower than rate with intraoperative RLN identification without neuromonitoring (2.6 per cent) or no RLN identification (6.3 per cent) ($P < 0.0001$). Detailed analysis of the complete spectrum of extent of resection and indications for surgery showed a positive trend for intraoperative neuromonitoring in comparison to the group with RLN identification without the use of neuromonitoring, but this trend was not statistically significant because of the small number of permanent RLN palsies.

Conclusion: Intraoperative neuromonitoring of the RLN has a beneficial effect for high-risk patients with recurrent goitre and thyroid carcinoma in whom the RLN is at greatest risk in cases of lobectomy or total thyroidectomy.

The 'false' non-recurrent inferior laryngeal nerve

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Background: A communication between the middle cervical sympathetic ganglion (MCSG) and the inferior laryngeal nerve (ILN) has been described. The anastomotic branch (sympathetic-inferior laryngeal anastomotic branch; SILAB) is usually thin, but is sometimes larger and has the same diameter as the ILN. The purpose of this study was to evaluate prospectively the frequency of this condition and its implications during neck exploration.

Methods: From November 1998 to October 1999, 791 neck explorations were performed: 677 for thyroid, 99 for parathyroid and 15 for concomitant lesions. Some 1253 ILNs were dissected: 656 (52.3 per cent) on the right and 597 (47.7 per cent) on the left side.

Results: The ILN was identified in all cases. On the right side a non-recurrent ILN (NRILN) was found in three patients (0.5 per cent) and a large SILAB in ten (1.5 per cent). No anomalous branch was found on the left side. The SILAB originated from the superior cervical sympathetic ganglion (SCSG) in two

patients and directly from the sympathetic chain (SC) above the MCSG in eight. No branch originating from the MCSG was found. The SILAB connected with the ILN less than 2 cm from the cricoid in all patients.

Conclusion: The SILAB may originate not only from the MCSG but also from the SCSG and directly from the SC. When the SILAB is as large as the ILN, it could be mistaken for a NRILN. Before concluding that the anomalous branch is a NRILN, one should check if it originates from the vagus or from the cervical sympathetic system. Awareness of this anatomical condition during neck exploration may help the surgeon to avoid injuries of an ILN running in the usual pathway.

Long-term prognosis of children with papillary thyroid cancer presenting with pulmonary metastases

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Background: Papillary thyroid cancer (PTC) has a generally favourable prognosis, but elderly patients with distant metastases or extracapsular invasion fair poorly. In small studies with short follow-up, young patients presenting with such extracapsular invasion and pulmonary metastases have fared well. This retrospective study was undertaken to clarify the long-term prognosis of such patients with advanced PTC.

Methods: Twenty-one children and young adults (median age 14 (range 6–20) years) presenting with PTC and pulmonary metastases were treated at a single institution between 1947 and 1998. Mean maximal tumour diameter was 4.65 cm. Initial surgical treatment consisted of total thyroidectomy ($n = 16$), subtotal thyroidectomy ($n = 4$) and isthmectomy ($n = 1$), coupled with a variety of lymph node dissections ($n = 20$). After operation, 19 patients were treated with ablative and incremental doses of iodine-131 until disease free. All patients were placed on suppressive thyroid hormone after operation. Mean length of follow-up was 21 years (range 3 months to 47 years). Follow-up was less than 3 years in four patients. All patients have undergone post-treatment radionuclide and radiological evaluation.

Results: Nine of the 21 patients developed recurrent disease. The risk of recurrence at 5 years was 39 (95 per cent confidence interval 14–57) per cent. Eight had cervical lymph node recurrence and no patient developed recurrent pulmonary disease. All patients with identifiable recurrent disease underwent selective lymph node resection, which involved multiple resections in four. At follow-up, 18 patients remain completely free of disease, one patient has recurrent cervical node disease and two patients have died. The disease-free survival at 5 years

was 95 (95 per cent confidence interval 86–100) per cent. Cause-specific death occurred in a single patient who died from extensive local disease at age 29 years after 12 years of multiple cervical lymph node recurrences.

Conclusion: A stepwise treatment approach including total thyroidectomy, high-dose iodine-131 treatment and early surgical reintervention for suspected local recurrent disease allows long-term survival and frequent 'cure' for young patients with PTC and concomitant pulmonary metastases.

Value of preoperative diagnostic modalities in patients with recurrent thyroid carcinoma

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Background: The prognosis of differentiated thyroid carcinoma is usually excellent, but the majority of patients who develop a recurrence have a higher risk of death from the disease. Beside clinical examination, several diagnostic tools, such as ultrasonography, ¹³¹I scanning, [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET) and thyroglobulin (TG) measurement under raised thyroid-stimulating hormone in serum can detect tumour recurrences. This prospective study compared the value of different diagnostic modalities in the detection of recurrent differentiated thyroid cancer.

Methods: From April 1992 to October 1999, 181 patients with thyroid carcinoma, of whom 150 had a well differentiated tumour, subjected to surgical treatment were identified prospectively. Some 107 patients (71 per cent) presented with primary tumour and 43 patients (29 per cent) with recurrent disease. The patients with tumour recurrence were evaluated regarding the mode of detection of recurrent disease, including clinical examination, ultrasonography, fine-needle biopsy (FNB), TG measurement and FDG-PET, the surgical treatment and outcome.

Results: Some 63 per cent of patients presented with regional lymph node metastases and 37 per cent with local recurrence. None of the patients with local recurrence was operated on for primary tumour in this department. In 87 per cent the recurrence was detected by clinical examination. Ultrasonography and ¹³¹I scan revealed suspicious findings in 97 and 69 per cent respectively. FNB disclosed abnormal cytological findings in 95 per cent. There were pathological TG levels in 86 per cent of patients. Among patients with a raised level of TG and negative scan results, 13 underwent FDG-PET, with pathological findings in 82 per cent.

Conclusion: In patients with well differentiated thyroid carcinoma, ultrasonography and FNB are the most sensitive methods for the detection of local recurrence or regional lymph node metastases. FDG-PET is a useful diagnostic tool in patients with a negative ¹³¹I scan and a raised level of TG.

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Medical management of bowel obstruction

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Bowel obstruction is a relatively common complication of advanced malignancy, particularly in gynaecological and gastrointestinal cancers. The symptoms (abdominal pain, constipation and vomiting) are most distressing for both patients and their carers. What should be the approach when faced with a patient with advanced malignant disease, for whom there is no further anticancer therapy available, who presents with bowel obstruction secondary to progressive disease? Surgery can provide valuable palliation in cancer-related bowel obstruction and no patient should be denied a surgical review. There are no defined guidelines for surgical intervention, however, and the management is to a large extent empirical. A recent systematic review has highlighted the wide variation in reobstruction, morbidity and mortality rates following surgery for malignant bowel obstruction¹. The reported rates of symptom control varied from 42 to 80 per cent.

How often is a decision to operate on a patient with established obstruction made on the grounds that there is presumed to be no alternative? I would suggest that medical management can be a realistic alternative and one that should be considered as an equal option in patients with bowel obstruction secondary to incurable and progressive malignant disease. This approach requires a move away from the classical surgical teaching of intravenous fluids, nil by mouth, nasogastric tube and serial radiographs. The alternative is symptom control with a range of drugs and medications, and the removal of many of the lines and tubes that so often tie a patient to a hospital bed, creating a barrier between the individual who is facing the inevitable reality of an impending death, and his family and friends.

As with many of the practices in palliative care, there is very little evidence on which to base the symptomatic treatment of bowel obstruction. There are, however, many reports of successful management in the literature since the first description by Mary Baines *et al.*² in 1985. As with the surgical series¹, there is no standard symptom control measure and no standard definition for 'successful palliation'. The following recommendations are based largely on experience, anecdote and expert opinion. It is very difficult to conduct controlled studies in malignant bowel obstruction; the patients are usually of poor performance status and difficult to recruit into trials³. Furthermore, the situation is often dynamic, changing from complete to partial obstruction

and back again with a significant incidence of spontaneous resolution³.

General principles

Considerable controversy surrounds the use of intravenous fluids in dying patients. One school claims that a patient's fluid requirements reduce dramatically during the terminal phase, and that fluid administration does not prolong life and will only exacerbate problems of fluid retention, toileting, pulmonary secretions and the need for suctioning⁴. Others claim that dehydration contributes significantly to drug toxicity, and to the confusion and agitation so often seen in dying patients⁵. In my experience, the repeated siting of intravenous lines and the biochemical monitoring that the giving of intravenous fluids requires is inappropriate in the dying. Diligent mouth care, mouth sponges, sucking ice and sips of fluid relieve thirst and provide comfort.

The widespread application of the subcutaneous route for the delivery of most essential drugs has revolutionized palliative care practices. It avoids the problem of obtaining and maintaining intravenous access for patients unable to tolerate food or fluid by mouth, and may permit discharge from hospital into community care if the patient so wishes. Relatives and carers may find it difficult to accept the removal of what are seen as 'life-lines' however, and subcutaneous fluids up to 2–3 litres a day (hypodermoclysis) can be given as a compromise. Eating is one of life's great pleasures and to deprive a dying patient of this enjoyment seems harsh. Patients should be allowed to eat small amounts of low-fibre food and to drink as tolerated, if they wish, even if this results in the occasional vomit. Some obtain great relief of symptoms following the placement of a nasogastric tube. Others loathe the idea of a plastic tube in the nose and prefer to vomit to relieve the build up of stomach contents. Repeated observations, fluid balance monitoring, radiographs and other investigations are pointless when they are not likely to change management.

Symptom control

There are no controlled studies but several case series have shown that the frequency of vomiting in bowel obstruction

can be reduced by various combinations of antiemetics⁶. Gastrokinetic agents (e.g. metoclopramide, cisapride) are usually avoided in those with bowel obstruction because of concern that they may exacerbate colic. However, some clinicians advocate their use because of the positive effect on gastric emptying, lower oesophageal sphincter pressure and antral contractility⁷. The antiemetics most commonly used are levomepromazine, cyclizine or haloperidol. All may be given subcutaneously although none is licensed for delivery by this route. Levomepromazine is a broad-spectrum antiemetic that acts at several of the 'emetic receptors' thought to be activated in bowel obstruction. Its sedative effect at high dose may be used to advantage in the terminal stages of disease⁸.

Pain associated with bowel obstruction is related both to abdominal distension and obstructed peristalsis causing 'colic'. Diamorphine is the opioid of choice for delivery by the subcutaneous route. There is no indication for using short-acting opioids such as pethidine and no evidence that pethidine is better than any other opioid for colicky pain⁹. Fentanyl, a synthetic opioid, is available in a transdermal delivery system, a skin patch that is changed every 72 h. It is appropriate for patients with stable pain, but as the drug takes 8–12 h to take effect and remains in a subcutaneous depot for up to 12 h following patch removal, it is not appropriate for dose titration. Antimuscarinics (e.g. hyoscine butylbromide) may be added for control of colicky pain either 'as required' by bolus dose or by a constant subcutaneous infusion.

There seems little logic in continuing with oral laxatives in established complete bowel obstruction. In incomplete or resolving obstruction, the practice should be to use 'softeners', such as docusate or MilPar[®] (liquid paraffin and magnesium hydroxide; Merck Consumer Health, Hull, UK) in an attempt to relieve constipation. Those laxatives whose primary action is by stimulation of the bowel (e.g. bisacodyl, danthron and senna) should be avoided as they may exacerbate colic. Rectal interventions (e.g. bisacodyl suppositories) may be used to 'unplug' an impacted rectum.

Dexamethasone is used commonly as an antiemetic and coanalgesic in palliative care. In some centres it is given to patients with bowel obstruction both to palliate symptoms and in an attempt to resolve the obstruction. The anti-inflammatory effect of steroids may reduce peritumour oedema associated with a malignant lesion and so free the obstruction. Any potential benefit must be balanced against the well known side-effects of steroid therapy (e.g. gastric irritation, agitation and exacerbation of diabetes). All three placebo-controlled trials that have addressed this issue have been limited by small sample size, but a recent meta-analysis of the pooled data points to a definite, albeit non-significant, benefit with respect to resolution of bowel obstruction in

favour of steroids¹⁰. Further studies are required to substantiate this but a short pulse of moderate-dose dexamethasone (8 mg/day for 5 days) is generally well tolerated and worth a trial.

Antisecretory antimuscarinic agents such as hyoscine butylbromide reduce intestinal motility and are licensed for the control of gastrointestinal smooth muscle spasm. They decrease gastric secretion and have been used for symptom relief in bowel obstruction. There are several reports of their benefit in reducing the number and frequency of vomits, and evidence exists of a reduction in the volume of fluids collected by nasogastric tube in patients with bowel obstruction¹¹.

Octreotide is a somatostatin analogue that reduces endocrine and exocrine secretion of the pancreas, stomach and intestine; by decreasing gut motility and secretions, it facilitates the absorption of water and electrolytes in the bowel. It is licensed for the relief of tumours associated with neuroendocrine neoplasia but is now widely used for the palliation of symptoms of bowel obstruction. There are multiple studies in the literature claiming dramatic improvements in patients with bowel obstruction, especially with respect to control of nausea and vomiting¹¹. Although side-effects are reported (nausea, abdominal cramps, diarrhoea and flatulence) this drug seems generally to be well tolerated. The development of long-acting somatostatin analogues given monthly by intramuscular injection may facilitate hospital discharge but the high cost of such drugs may be prohibitive.

In some situations, the above measures will fail to provide adequate or acceptable symptom relief. In this case a venting procedure might be considered. It is crucial that the patient understands that, although such a manoeuvre might allow them to eat and drink as they wish, it is a palliative procedure that will not result in effective feeding.

If death is inevitable, it does seem less than ideal to be attached to lines and bleeping machines, with a painful laparotomy scar, needles in the arm and a plastic tube up the nose. There is another scenario. It is possible for a dying patient in complete bowel obstruction to spend the last few days of life with family and friends, with symptoms controlled by medical management and good palliative care.

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Politics in surgical publishing

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So far, this series has dealt with factors involving primarily the surgeon-cum-writer. These are the *abcs*, so to speak, of getting started: 'why' to publish an academic surgery paper, and 'what' and 'where' and 'how'. Despite the fact that these aspects of publication create the substance and 'guts' of any paper, they are not the only determinants of the success or failure of a publication effort.

Beyond the individual surgeon-author's efforts or control is the real-world consideration of virtually every social interaction—politics. Politics has been variously defined as 'the art and science of government' and 'intrigue and manoeuvring within a group'. Politics affects academic publishing when individuals, in one way or another, attempt to exert influence on policy or outcome based on personal interests or biases. Politicking, as such, can be manifest from the author's side of the publishing interaction or from the journal's.

Politics in the author's camp

Authorship

The politics of publishing is perhaps nowhere more obvious than in the assignment of authorship. While the person who conceives an idea, gets the funding and does the most work is indisputably entitled to first authorship, other individuals who are granted coauthorship by no means always contribute equitably.

In a nod to patriarchy, the senior faculty member or division/department Chair is frequently made a coauthor on studies to which he or she has made no discernible contribution. This may be academic homage, but it is not honest. The name of a senior faculty member who *bas* contributed to a study is customarily listed last in the order of authors. Other individuals contributing to the study are generally listed after the first author, in descending order of the contribution made.

Others may be awarded coauthorship as a personal thank you, such as individuals representing commercial sponsors for research. The bottom line is that authorship should never be 'for sale'. It must be reserved only for those who

make an active and substantial contribution to the study being reported.

This prescript extends to the unsavoury practice of including as authors individuals whose professional renown will add credibility to the work but who have no knowledge of the work or of the use to which their names are being put. People who do this may believe it is a win-win situation, with the unwitting author having another publication to his or her name. In fact, it constitutes fraudulent use of someone else's reputation and, in fact, the person whose name has been used might well find substantial fault with the work being proffered.

Duplicate publication and 'salami-slicing'

Salami-slicing is the practice of cutting up a body of data to yield several papers where one complete paper would be optimal. It may also be used to give several participants in a study a chance at first authorship, often in different specialty journals. Duplicate publication, submitting the same (or substantially the same) study to more than one journal, is done for the same reason. In a system based on quantity rather than quality of papers published, researchers boost their 'counts' by spreading the word as far as it will go.

While the dishonesty inherent in falsifying data is obvious, many people wink at duplicate publication and even more so at 'salami-slicing'. Although acknowledging that these practices are unethical, George Lundberg, former editor of *The Journal of the American Medical Association*, described the differences as follows. If falsifying data is 'a felony with intent to commit vehicular homicide, then duplicate publication would be a traffic ticket'¹. Nevertheless, such 'misdemeanours' are not without price.

Although all reputable journals have policies against these practices, their prevalence is all too widespread—up to 25 per cent of the published literature by some estimates². So what's the harm? For one, it is an ongoing problem for editors who are constantly wrestling with publisher-imposed page limitations, and with the professional and ethical responsibility to optimize the use of available pages. Scientifically, redundant publication is detrimental since it tends to overestimate the effects of whatever drugs, techniques or interventions are being discussed. Such

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distortions may lead to misuse of the proposed treatments, or misallocation of research and clinical resources. This short-changes everyone.

Politics in the journal's camp

Peer review process

At its best, 'peer review weeds out bad studies and recognizes good ones'³ but the process is far from perfect.

Reviewers may be biased. For example, they might downgrade a manuscript sent to them for review if the content of the paper contravenes what they themselves practise. Or they may be biased in favour of (or against) a particular institution or researcher. One study showed that editors and reviewers favoured prestigious authors, and made more allowances for male authors⁴. A solution would be to double-blind the review process or to open it up completely. This issue is not likely to be resolved in the immediate future.

Reviewers may lack the expertise to evaluate a paper sent to them. Science has become so specialized that even professionals in the same field may well not be knowledgeable about a subspecialty area. Yet it is the perversity of human nature – and surgeons are surely not immune – that we are loath to admit ignorance, especially in situations in which professional egos may be on the line. To those reviewers who are notable exceptions and let us know that they are out of their professional depth for reviewing a particular manuscript, we tip our hats and extend our admiration.

Reviewers may be too busy to provide a careful review. Many of the best known academic surgeons are asked to serve on many editorial boards and they seldom decline. The process would be better served by including more, perhaps less well known but highly capable, surgeons. Those asked to review papers for top surgery journals are generally the most professionally active, frequently with 70-h working weeks and still not enough time to accomplish everything. A request from a journal editor to review a manuscript or to serve on the editorial board, although flattering, is one more responsibility on already overflowing plates. A recent study showed that review quality increased with increasing time spent on the review, up to but not more than 3 h⁵.

It is the editor's responsibility to resolve any questions of review quality, thoroughness or fairness, usually by obtaining additional reviews.

Commercial sponsorship of submitted works

Financial pressures to order the medical agenda also exist in the form of for-profit sponsorship of medical research. It is

an irony of drug regulation that the burden of proof of safety and effectiveness rests with the very companies (pharmaceutical or medical device) that stand to profit most. Perhaps because of this, pharmaceutical companies and manufacturers of medical devices offer financial support to academic scientists for expert evaluation of new products. But such academic partnerships also lend prestige and credibility to the commercial sponsor, warranted or not.

The political challenges are clear. On the one hand, the researcher who accepts support money from a commercial sponsor must take scrupulous care to remain scientifically objective and not succumb to the temptation to identify with the benefactor. The researcher must also resist the temptation to reward financial support with authorship. When the results of a commercially sponsored study are submitted for consideration to a peer-reviewed journal, it must be identified as such. On the other side of the publishing equation, the journal editor must take great care that the sponsorship of any study is clearly stated on the first printed page so that readers can take that into account when deciding on the work's validity. The editor also has the obligation to question authorships if any doubt exists as to propriety.

The editor

Editors and referees, it has been said, are the 'gate-keepers' of science⁶. They have also been variously accused of ignorance, carelessness and even deliberate obstructiveness; of conceptual inbreeding; and gaining an unfair research advantage by having advance access to new research. The truth is more mundane, being somewhere between the exalted and the damned. Editors do help set the medical agenda; it is intrinsic to the job.

Editors choose who will review a paper and, as Arthur Baue pointed out⁷, 'the fate of a manuscript can be determined by the selection of reviewers'. A conscientious editor will be aware of the shortcomings as well as the strengths of potential reviewers and will try to achieve a balance. Although the decision to accept or reject a manuscript is often clear, there are many borderline cases and the editor holds ultimate sway over what gets published and what does not.

When, in spite of our best attempts to be fair, an author of a rejected manuscript requests (or sometimes demands) reconsideration, we need to be very honest with ourselves and decide whether there is a legitimate gripe, and proceed accordingly. Not often, but at least on several occasions, truly excellent manuscripts have emerged from this sequence of rejection–reconsideration–acceptance.

The editor's agenda-setting function also extends to who is invited to be a member of the editorial board.

This can influence not only what individual papers get published, but what scientific interests and subspecialties are emphasized.

Finally, perhaps the most politically blatant scenario of the editorial office occurs when a prominent academician attempts to influence an editorial decision to accept, or to advance the priority of, a paper in assignment for publication.

Conclusion

It has been suggested that the social context of science operates to control the communication of science⁸. This is but another way of saying that politicking is as inevitable in scientific publishing as it is in any human enterprise. What we must remember, whether as authors or as editors, is that temptations will always exist to advance our more self-serving aims, whether they be small or large. What we must strive for, consciously and consistently, is intellectual honour. The greater good hangs in the balance.

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Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

Dealing with misconduct

Principles

The general principle confirming misconduct is intention to cause others to regard as true that which is not true.

The examination of misconduct must therefore focus, not only on the particular act or omission, but also on the intention of the researcher, author, editor, reviewer or publisher involved.

Deception may be by intention, by reckless disregard of possible consequences, or by negligence. It is implicit therefore that 'best practice' requires complete honesty, with full disclosure.

Codes of practice may raise awareness, but can never be exhaustive.

Investigating misconduct

Editors should not simply reject papers that raise questions of misconduct. They are ethically obliged to pursue the case. However, knowing how to investigate and respond to possible cases of misconduct is difficult.

COPE is always willing to advise, but for legal reasons, can only advise on anonymised cases.

It is for the editor to decide what action to take.

Serious misconduct

Editors must take all allegations and suspicions of misconduct seriously, but they must recognize that they do not usually have either the legal legitimacy or the means to conduct investigations into serious cases.

The editor must decide when to alert the employers of the accused author(s).

Some evidence is required, but if employers have a process for investigating accusations — as they are increasingly required to do — then editors do not need to assemble a complete case. Indeed, it may be ethically unsound for editors to do so, because such action usually means consulting experts, so spreading abroad serious questions about the author(s).

If editors are presented with convincing evidence — perhaps by reviewers — of serious misconduct, they should immediately pass this on to the employers, notifying the author(s) that they are doing so.

If accusations of serious misconduct are not accompanied by convincing evidence, then editors should confidentially seek expert advice.

If the experts raise serious questions about the research, then editors should notify the employers.

If the experts find no evidence of misconduct, the editorial processes should proceed in the normal way.

If presented with convincing evidence of serious misconduct, where there is no employer to whom this can be referred, and the

author(s) are registered doctors, cases can be referred to the General Medical Council.

If, however, there is no organization with the legitimacy and the means to conduct an investigation, then the editor may decide that the case is sufficiently important to warrant publishing something in the journal. Legal advice will then be essential.

If editors are convinced that an employer has not conducted an adequate investigation of a serious accusation, they may feel that publication of a notice in the journal is warranted. Legal advice will be essential.

Authors should be given the opportunity to respond to accusations of serious misconduct

Less serious misconduct

Editors may judge that it is not necessary to involve employers in less serious cases of misconduct, such as redundant publication, deception over authorship, or failure to declare conflict of interest. Sometimes the evidence may speak for itself, although it may be wise to appoint an independent expert.

Editors should remember that accusations of even minor misconduct may have serious implications for the author(s), and it may then be necessary to ask the employers to investigate.

Authors should be given the opportunity to respond to any charge of minor misconduct.

If convinced of wrongdoing, editors may wish to adopt some of the sanctions outlined below.

Sanctions

Sanctions may be applied separately or combined. The following are ranked in approximate order of severity:

A letter of explanation (and education) to the authors, where there appears to be a genuine misunderstanding of principles.

A letter of reprimand and warning as to future conduct.

A formal letter to the relevant head of Institution or funding body.

Publication of a notice of redundant publication or plagiarism.

An editorial giving full details of the misconduct.

Refusal to accept future submissions from the individual, unit, or Institution responsible for the misconduct, for a stated period

Formal withdrawal or retraction of the paper from the scientific literature, informing other editors and the indexing authorities.

Reporting the case to the General Medical Council, or other such authority or organization which can investigate and act with due process.

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Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon

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Background: The development and anatomy of Denonvilliers' fascia have been controversial for many years and confusion exists about its operative appearance. Better appreciation of this poorly understood anatomy, and its significance for impotence after rectal dissection, may lead to further functional improvements in pelvic surgery.

Method: A literature review of Denonvilliers' fascia and impotence after pelvic rectal surgery was undertaken.

Results: Denonvilliers' fascia has no macroscopically discernible layers. The so-called posterior layer refers to the fascia propria of the rectum. The incidence of erectile and ejaculatory dysfunction after rectal excision is high in older patients, and when performed for rectal cancer. There is no consensus about the relationship of Denonvilliers' fascia to the plane of anterior dissection for rectal cancer.

Conclusion: Colorectal surgeons should focus on the important anatomy between the rectum and the prostate to improve functional outcomes after rectal excision. A classification of the available anterior dissection planes is proposed. Surgeons should be encouraged to document the plane used as well as outcome in terms of sexual function.

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Introduction

The anatomy of Denonvilliers' fascia has been disputed for many years. This has become important as colorectal surgeons become ever more concerned with pelvic surgical anatomy in terms of its relevance for improving not only the oncological but also the functional outcome of surgery. Although the term Denonvilliers' fascia is often used in descriptions of operations, its precise nature varies from patient to patient, and surgeons are at times unsure of the exact relationship between their operative plane and the fascia itself.

Embryology of Denonvilliers' fascia

In 1836 Denonvilliers reported his discovery of a 'prostato-peritoneal' membranous layer between the rectum and seminal vesicles^{1,2}; he later described this layer in more detail³. Cunéo and Veau⁴ suggested that the tissue Denonvilliers had described developed from fusion of the embryonic peritoneum of the rectovesical cul-de-sac, citing

reports of perineal hernias and developmental cysts. Zuckerkandl had shown that the embryonic cul-de-sac extended to the pelvic floor. Elliot Smith supported this theory after undertaking pelvic dissections in fetuses and adults^{5,6}.

In the early 1920s Wesson^{7,8} disputed the peritoneal fusion theory, proposing that a condensation of the layers of embryonic mesenchyme found over the rectum and bladder led to the adult Denonvilliers' fascia. On the other hand, Tobin and Benjamin⁹ presented persuasive histological evidence to support the peritoneal fusion theory. In embryos of various stages of development they saw Wesson's mesenchymal tissue, but found that this later differentiated into muscle and connective tissue. They discovered a layer of mesothelium adjacent to mesenchyme, and called this peritoneum. They showed that this was the pelvic peritoneal continuation of the embryonic cul-de-sac, which regressed and approached the vesicles as its caudal end fused. The peritoneal mesothelium disappeared, leaving the mesenchyme as a fibrous membrane which becomes Denonvilliers' fascia in

the adult. This embryological process is identical to that described by Toldt for development of intestinal peritoneum^{10,11}.

Tobin and Benjamin⁹ observed that Wesson's rectal mesenchymal layer developed into the fascia propria of the rectum, which Denonvilliers had correctly identified as a layer separate from his fascia. This was a critically important distinction as previously the two layers had been referred to rather loosely. However, as this tissue was now considered part of Denonvilliers' fascia in the clinical literature, Tobin and Benjamin designated it the posterior layer of Denonvilliers' fascia, even though it had a different embryological origin. Unfortunately, this has led to persistent confusion about the existence of two layers of the fascia. The result has been conflicting opinion on the anatomy of Denonvilliers' fascia and its relationship to the anterior plane of rectal dissection required during total mesorectal excision (TME).

In 1993, Richardson¹² elegantly demonstrated a dense double layer of elastin in the rectogenital septum on electron micrography, and in 1994 a rare case of cystic mesothelioma, arising below the pelvic peritoneum and behind the prostate, was described¹³, adding further weight to the concept of peritoneal fusion.

Although Denonvilliers' original description gave no account of the presence of such a membrane in a female, there is little doubt that the rectovaginal septum is the female counterpart, and is a normal, constant structure. Heald and Moran¹⁴ stated that in women the fascia is less obvious but, importantly for the conduct of rectal dissection, it provides mobility for the rectum on the posterior vaginal wall.

Surgical anatomy of Denonvilliers' fascia

The appearance of the fascia at operation varies considerably, from a fragile translucent layer to a tough leathery membrane¹⁵; there is debate about how frequently it can be identified. It is more prominent in younger patients, becoming less so with increasing age. It is often more obvious after preoperative radiotherapy to the pelvis or where there is transmural rectal inflammation, for example in Crohn's disease. It is certainly more obvious and substantial than the fascia propria of the rectum, which is a thin membrane enveloping the mesorectum¹⁵. Histologically, Denonvilliers' fascia is composed of dense collagen, smooth muscle fibres and coarse elastic fibres. It is related to the prostate and seminal vesicles anteriorly, and to the rectal wall, the thin anterior mesorectum and the fascia propria posteriorly (*Fig. 1*).

Both gross anatomical and surgical descriptions have been surrounded by confusion. Goligher¹⁶ described the

fascia as being more closely adherent to the rectum than to the prostate. Urological descriptions usually refer to the fascia as dense, easily identified and closely applied to the prostate and seminal vesicles¹⁷. Church *et al.*¹⁵ noted that the fascia is more densely applied to the prostate than to the rectum, and that references to the 'posterior' layer of the fascia actually describe the fascia propria of the rectum. Heald and Moran¹⁴ described Denonvilliers' fascia as constituting the anterior surface of the mesorectum, lying on the rectal side of the plane in which TME surgery is conducted. They outlined a distinct plane separating this shiny fascia and the seminal vesicles. Therefore TME surgery would, by definition, resect Denonvilliers' fascia. Nano *et al.*¹⁸ contended that the fascia 'represents a plane of cleavage both with the rectum and between the two leaves that make it up', and that 'the anterior leaf of the fascia is closely applied to the seminal vesicles'. Moriya *et al.*¹⁹ stated that in rectal cancer the fascia must remain adherent to the rectum. Some authors still recognize a so-called 'posterior layer' of Denonvilliers' fascia. A recent histological study suggests that Denonvilliers' fascia is more closely adherent to the prostate, and is found in rectal cancer specimens only when deliberately taken for specific oncological reasons, for example, the anterior circumferential radial margin being threatened by anterior rectal quadrant tumour involvement²⁰.

Surgical anatomy of the autonomic nerves of the pelvis

Superior hypogastric plexus

The superior hypogastric plexus is a network of sympathetic fibres situated just below the aortic bifurcation. Above it is continuous with the sympathetic trunks and caudally fibres exit as the hypogastric nerves, which unite the superior and inferior hypogastric (pelvic) plexuses.

Hypogastric nerves

Just above the pelvic brim slightly left of the midline, the superior hypogastric plexus bifurcates into the 2–3-mm diameter hypogastric nerves and these lie 1–2 cm medial to the ureters along the posterolateral wall of the pelvis. The nerves lie superficially in the plane between the peritoneum and the endopelvic fascia²¹. At this level the nerves contain purely sympathetic fibres. The rectum and mesorectum are invested in a smooth layer of fascia propria which lies in the plane immediately anterior to these nerve trunks. The trunks are plastered to the posterolateral aspect of the mesorectum by small unimportant rectal branches of these nerves and so are at risk

at the beginning of rectal mobilization. The hypogastric nerves eventually leave the posterolateral aspect of the mesorectum for the pelvic side wall, coming to lie deeper in relation to the peritoneum.

Nervi erigentes

The pelvic parasympathetic (splanchnic) nerves (nervi erigentes) arise from the sacral roots of S2, S3 and S4. They pierce the endopelvic fascia from behind to enter the plane of the pelvic plexus. The pelvic parasympathetics join

the sympathetic hypogastric nerve in a Y-shaped connection to form the pelvic plexus²².

Pelvic plexus

The pelvic plexus is a network of nerves forming a sheet of neural tissue that lies quite lateral in the pelvis, lateral to the lower third of the rectum¹⁸. The lateral ligament of the rectum is described in textbooks as arising from the endopelvic fascia of the side wall and inclined antero-medially as it approaches the rectum. However, in recent

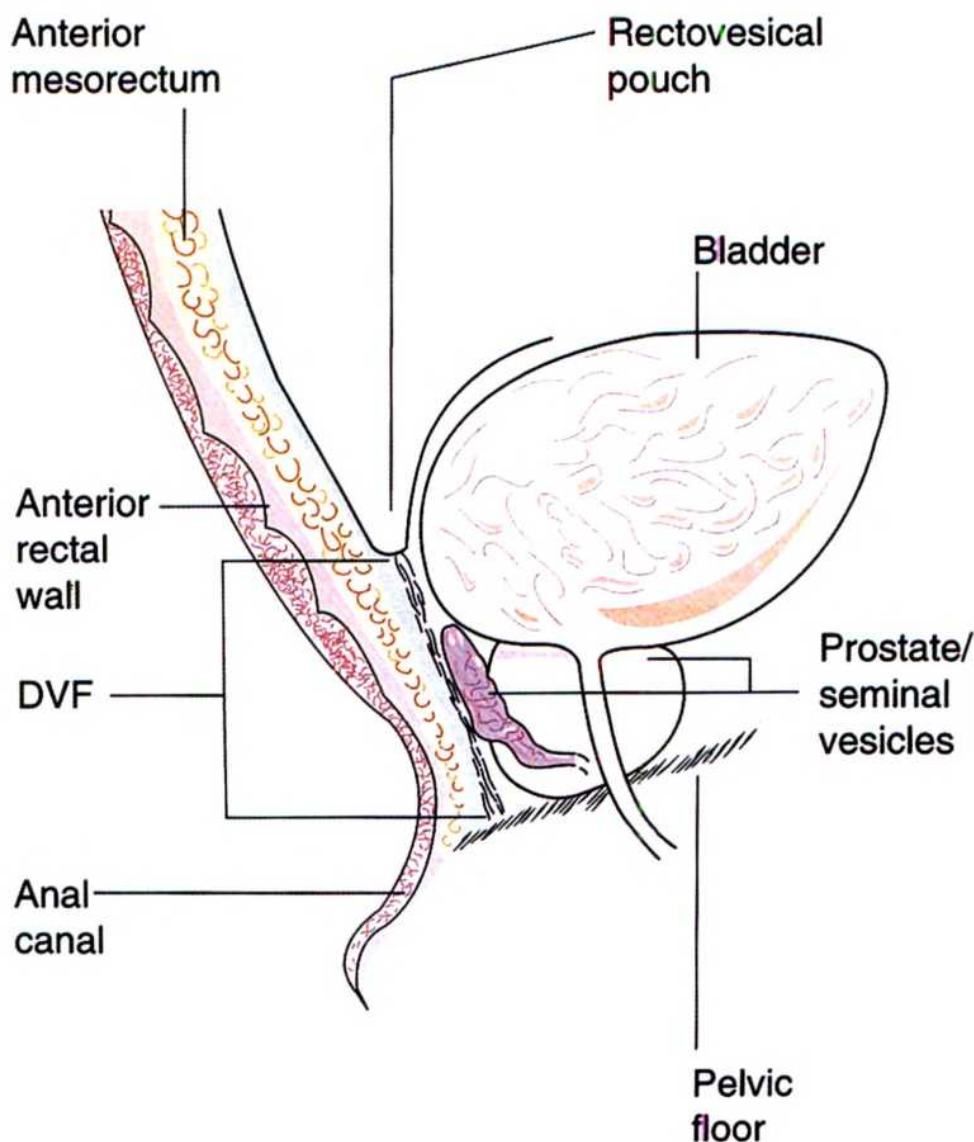


Fig. 1 Lateral view of Denonvilliers' fascia (DVF) and its relationships

years colorectal surgeons have questioned the existence of discrete anatomical lateral ligaments; a recent cadaver study has supported this doubt²³. Many studies have shown that a middle rectal vessel exists only in about 25–50 per cent of cases and is almost never greater than 2 mm in diameter^{23–27}. The vessel courses medially towards the lower rectum just above the pelvic floor to run near the ipsilateral seminal vesicle and apex of the prostate²⁵.

Cavernous nerves

The layout of the nerve fibres in the pelvic plexus responsible for different functions has been studied in some depth^{22,28–30}. Branches from the pelvic plexus to the rectum run lateral to medial immediately under the peritoneum. Nerves from the plexus to the bladder and sexual organs run deeper and are inclined more anteriorly²². The cavernous nerves run in neurovascular bundles at the lateral border of Denonvilliers' fascia^{31,32}. These nerves eventually run anterior to Denonvilliers' fascia at the posterolateral border of the apex and base of the prostate, but are closely related to the anterior wall of the rectum. The precise relationship of the neurovascular bundles and cavernous nerves to Denonvilliers' fascia has been questioned recently by Kourambas *et al.*³³.

Urological aspects

Impotence after pelvic surgery has concerned urologists ever since Young described the first perineal prostatectomy in 1905³⁴. Radical prostatectomy has, until recently, rendered most patients impotent³⁵. We have urologists to thank for our refined understanding of the anatomy of the pelvis plexus and cavernous nerves. Detailed studies to determine this anatomy and the aetiology of impotence after radical prostatectomy have been conducted in recent years by Walsh and co-workers^{32,36} and confirmed by Lue *et al.*³⁷. Walsh *et al.* concluded that impotence resulted from damage to the cavernous nerves, either at the lateral pedicles or when dividing the urethra. Before this, the precise anatomical location of these nerves was unknown. These authors drew three main anatomical conclusions. First, a prominent neurovascular bundle is located at the posterolateral border of the apex and base of the prostate. The visible nerves in this bundle branch to give rise to the microscopic cavernous nerves. Second, the neurovascular bundles are consistently found in the leaves of the lateral pelvic fascia outside the prostatic capsule, at the lateral edge of Denonvilliers' fascia. The bundles and prostatic capsule are separated by only 1.5–3 mm at the base and apex of the prostate respectively. Third, the nerves in the neurovascular bundles are intimately associated with vessels. These vessels

provide a visible landmark to identify the bundles and are generally oriented lateral to the nerves.

The technique of 'nerve-sparing' radical prostatectomy evolved as a modification of the original procedure in the light of the above findings^{36,38}. The published series of this newer, more precise procedure describe lower rates of impotence (32–35 per cent)^{39,40}.

Sexual dysfunction after colorectal surgery

The risk to potency occurs during rectal dissection, as the pelvic autonomic nerves are intimately related to the rectum. Rectal dissection, particularly for low rectal cancer in men, presents a difficult challenge. The narrow male pelvis, the low level of the tumour and the dictates of proper oncological clearance conspire to jeopardize the nerves governing erectile and bladder function.

Sexual dysfunction after pelvic surgery is characterized by erectile dysfunction or impotence, and ejaculatory dysfunction. Impotence may be partial or complete, temporary or permanent. Ejaculatory dysfunction consists of absent ejaculation, retrograde ejaculation and painful ejaculation.

There is a physical component to these dysfunctions, essentially one of degrees of damage to the sympathetic and parasympathetic nerves. Comorbid factors such as vascular disease, diabetes and ageing may contribute. There may also be a psychological component, harder to quantify, with concerns about the underlying disease, surgery and the presence of a stoma⁴¹ playing a part. Age is an important factor. It is known that the incidence of impotence increases with age; it may be that diminished function or 'reserve' makes neural damage more likely, or surgical damage may precipitate a sudden decline in function that was already on the threshold of decline.

Incidence, assessment and definition

Permanent impotence in men occurs in 17–100 per cent of cases after abdominoperineal excision of rectum (APER) and in 0–49 per cent after anterior resection of rectum (AR) for rectal cancer^{42–59}. These wide-ranging rates reflect, among other factors, variations in case-mix, evaluation of dysfunction, study design and definitions, as well as technique and expertise.

There are difficulties in analysing the literature. All data have been gathered subjectively by either interview or patient questionnaire. These techniques are somewhat unreliable, but no objective measure of potency has so far been reported in the colorectal literature. Most data are retrospective and this creates problems of recall bias.

Patients who are sexually inactive are often not well accounted for. While the frequency of sexual intercourse is known to decrease with advancing age^{60,61}, those who are sexually inactive may be so as a direct consequence of surgery.

No standardized definition of impotence or instrument for its measurement has been reported in the literature. This makes comparison between published series difficult. However, there now exists a standardized, widely accepted and validated sexual function questionnaire, the International Index of Erectile Function⁶². This could be used in future studies of sexual function which should allow easier comparison between series.

Anterior resection *versus* abdominoperineal resection

The incidence of sexual dysfunction after APER is higher than that after AR (*Table 1*). APER is perceived to be more radical for lower tumours than sphincter-saving surgery. Santangelo *et al.*⁴⁹, in a study of men aged less than 60 years, described an incidence of permanent impotence of 44 per cent after APER and 25 per cent after AR. However, if these cases were divided into high and low AR, the incidence was 0 and 33 per cent respectively. In addition, the presence of a permanent stoma may have some psychological bearing on erectile function, although there is evidence to refute this⁴¹.

Wide pelvic lymphadenectomy

Wide pelvic lymphadenectomy has enjoyed some popularity in Japan in an attempt to reduce local recurrence; impotence affects 23–100 per cent of patients^{63–71}. A modified 'nerve-sparing' procedure has now been described but the incidence of impotence remains high¹⁹. Lateral node dissection yields positive nodes in only 10–15 per cent of patients^{68,69}; local recurrence rates of 4 per cent, and a 5-

year survival rate of 78 per cent in patients with Dukes' B and C tumours, have been reported after TME⁷². It is unlikely that patients accrue enough benefit to justify these high rates of impotence as well as the possibility of bladder dysfunction.

Proctectomy for benign disease

The rate of impotence after rectal excision for inflammatory bowel disease is lower than that after excision for rectal cancer (*Table 2*), the incidence of impotence ranging from 0 to 25 per cent^{41,42,58,63,73–100}. Patient age is an important factor. The incidence of sexual dysfunction after operation increases with age and, in general, the mean age of patients with inflammatory bowel disease having surgery is about 20 years less than that of patients with rectal cancer^{42,64}. Surgical technique may also differ, with the close rectal plane of dissection sometimes being used in an effort to minimize the risk to the pelvic nerves^{16,83,84}. More commonly the mesorectal plane is used.

Sexual dysfunction in women

Sexual dysfunction after rectal excision has been less frequently studied in women than in men, partly owing to the relatively greater ease of measurement of dysfunction in men. There is a poorer understanding of postoperative sexual dysfunction in women. Most papers have focused on infertility, childbirth and dyspareunia, with a lack of attention to the effect of pelvic nerve damage on female sexual function^{101,102}. A few studies^{103,104} have addressed neurological damage as a cause of problems such as inability to attain orgasm, and reduced vaginal sensitivity and lubrication, but the dysfunctional outcomes of pelvic nerve damage in women corresponding to those in men that produce erectile and ejaculatory dysfunction are poorly understood.

Table 1 Summary of published series on sexual dysfunction rate after conventional rectal excision for cancer: influence of type of resection

Operation	No. of patients	Loss of ejaculation	Partial impotence	Complete impotence	Total impotence
APER	494	96 of 332 (29)	38 of 281 (14)	78 of 301 (26)	250 of 494 (51)
AR	224	51 of 217 (24)	8 of 89 (9)	10 of 109 (9)	63 of 214 (29)

Values in parentheses are percentages. The totals may not add up owing to selective publication rates. Data are from six prospective and 12 retrospective studies^{42–59}. APER, abdominoperineal excision of rectum; AR, anterior resection of rectum

Incidence of bladder dysfunction

The incidence of permanent bladder denervation after rectal excisional surgery ranges from 0 to 19 per cent (Table 3)^{43,44,105–110}. The urodynamic features of bladder denervation have been well described^{111,112}, and consist of some or all of the following dysfunctions of parasympathetic, sympathetic and somatic supply: reduced bladder compliance during filling, detrusor hypocontractility, bladder neck incompetence and reduced urethral closure pressure. The partial lesion, which quite often is reversible after several months, is characterized by early lowering of bladder compliance with intact detrusor contractility. The complete lesion is characterized by a loss of detrusor contractility. Although the numbers in collected series are small, it appears that bladder dysfunction is more likely after APER than after AR (Table 3).

Effect of radiotherapy

Primary radiotherapy for localized prostate cancer causes impotence in 5–40 per cent of patients¹¹³. Although the treatment field and volume, among other factors, may be different from that for rectal cancer, anecdotal evidence suggests that radiotherapy contributes to postoperative impotence.

Sites of risk of nerve damage

One of the difficulties in preventing nerve damage during rectal excisional surgery is that it is difficult to be specific about where most injuries take place. Nevertheless, four key zones exist, one in the abdomen and three in the pelvis.

Inferior mesenteric artery origin

The risk in the abdomen occurs during ligation of the pedicle of the inferior mesenteric artery, particularly if this is done flush at the aorta. The purely sympathetic hypogastric nerves are vulnerable here.

Posterior dissection

The first pelvic zone of risk is in the posterior plane of rectal dissection. Anatomical dissection of the rectum is carried out in the loose areolar connective tissue immediately outside the fascia propria, and the nerves lie just outside this plane. They are easily damaged if the correct plane is not entered, if blunt dissection is used without regard to the proximity of these nerves, or if bleeding is not rigorously controlled and good direct vision is lost. The damage is purely sympathetic at this level as the nervi erigentes have not yet joined the bundle.

Lateral dissection

The second pelvic zone relates to lateral dissection. Straying laterally out of the mesorectal plane may injure the pelvic plexus, particularly if excess traction is placed on the rectum, tenting the plexus superiorly and medially³⁰. Radical lymphadenectomy procedures, as practised in Japan, may lead to nerve injury in this zone. The pattern of nerve damage here and beyond the pelvic plexus tends to be mixed sympathetic and parasympathetic. Given recent anatomical findings of a relatively insignificant contribution from a small, often unilateral, middle rectal artery and the waning concept of the lateral ligaments as distinct anatomical structures, significant reduction of damage in this zone may be possible²³. Avoidance of both 'hooking' of

Table 2 Summary of published series of sexual dysfunction rate after rectal excision: influence of benign *versus* malignant disease

	No. of patients	Loss of ejaculation	Total impotence
Benign	2535	59 of 1996 (3)	77 of 2535 (3)
Malignant	744	116 of 489 (24)	325 of 744 (44)

Values in parentheses are percentages. Data are from 17 prospective and 32 retrospective series relating to benign^{41,42,55,73–100} and malignant^{42–59} disease

Table 3 Summary of published series of bladder dysfunction rate after conventional rectal excision for cancer (both sexes): influence of type of resection

Operation	Temporary denervation	Partial permanent denervation	Complete permanent denervation
APER	22 of 96 (23)	0 of 71 (0)	16 of 96 (17)
AR	8 of 190 (4)	2 of 66 (3)	9 of 256 (4)
Mixed	—	5 of 41 (12)	3 of 41 (7)
Total	30 of 286 (10)	7 of 178 (4)	28 of 393 (7)

Values in parentheses are percentages. Data are from six prospective and two retrospective studies^{43,44,101–106}. APER, abdominoperineal excision of rectum; AR, anterior resection of rectum

the lateral tissue with the finger and clamping of the middle rectal pedicle may help achieve this²³.

Anterior dissection

The third pelvic zone of risk is during anterior rectal dissection. There is a very narrow space between the rectum and the prostate and seminal vesicles. During deep dissection of the anterior extra-peritoneal rectum away from the prostate and seminal vesicles, or during haemostasis in this difficult to access area, the cavernous nerves are at risk. This is probably where most parasympathetic nerve damage occurs, and may explain why impotence is more common the deeper the pelvic dissection goes (high AR *versus* low AR *versus* APER).

Planes available for anterior rectal dissection

A consensus has generally been reached about the anatomy of the plane of posterior and lateral rectal dissection, but this is not so anteriorly. What planes are available to the surgeon anteriorly? Can the surgeon easily differentiate them? Which should be used and when? Three planes exist and dissection within them involves resection of none, some or all of the structures lying between the anterior rectal wall and the prostate and seminal vesicles. These structures include the anterior mesorectum, fascia propria of the rectum and Denonvilliers' fascia; the anterior plane of dissection may not necessarily be the same plane in which the posterior and lateral dissection is conducted.

It is important to remember that the distinction between these planes can be difficult at operation; the distance between the anterior rectal wall and the prostate and seminal vesicles is short, and the anterior mesorectum is thin. Not only are the differences between these surgical planes subtle, but access for dissection under direct vision in a man is often restricted. However, the close proximity of vital nerves and the importance of gaining maximal local control in rectal cancer makes the distinction of planes important.

The authors propose a classification of anterior dissection planes that would enable surgeons to communicate their surgical technique with improved precision, allowing data between centres to be compared more easily. Use of the terms close rectal, mesorectal and extramesorectal to describe the available anterior planes is suggested. Such detail of anterior dissection could be documented in the operation note using such a classification. It should also be possible to confirm histologically

which anterior plane has been used. These planes are now described in more detail.

Close rectal plane

The close rectal plane (previously called perimuscular) is shown diagrammatically in Fig. 2. This plane lies immediately on the rectal musculature, but inside the fascia propria of the rectum. It is not an anatomical plane, and so dissection within the anterior mesorectum may be slightly more difficult and bloody than in the mesorectal plane¹⁵. Multiple blood vessels cross this plane to enter the rectal wall, which may occasionally be inflamed. Anteriorly, bleeding is usually quite easy to control using diathermy.

Mesorectal plane

The mesorectal plane immediately outside the fascia propria may be entered by continuation of the same plane of dissection from the posterior and lateral aspects. It is a natural anatomical plane that should be familiar to the colorectal surgeon. However, anteriorly this plane is slightly less obvious than posteriorly and laterally. Dissection in this plane will separate the fascia propria of the rectum, with its enclosed anterior mesorectum, from Denonvilliers' fascia, which is left intact on the prostate and seminal vesicles.

Extramesorectal plane

Use of the extramesorectal plane permits a resection of Denonvilliers' fascia anteriorly, staying immediately on and exposing the prostate and seminal vesicles. As dissection is conducted in a plane anterior to Denonvilliers' fascia, the risk of damage to the cavernous nerves is theoretically high. The distinction between this plane and the mesorectal plane may not be straightforward.

Appropriate plane of anterior rectal dissection

In benign disease the choice is relatively simple. All surgeons will agree to stay posterior to Denonvilliers' fascia¹⁵; some will favour close rectal dissection, but this may be technically more difficult. There is evidence now that close rectal dissection does not protect the pelvic nerves any more than mesorectal dissection¹⁴.

In malignancy the choice is less straightforward. Some recommend taking Denonvilliers' fascia, thus using the extramesorectal plane¹⁹. Others claim to stay anterior to the fascia behind the bladder, then posterior behind the

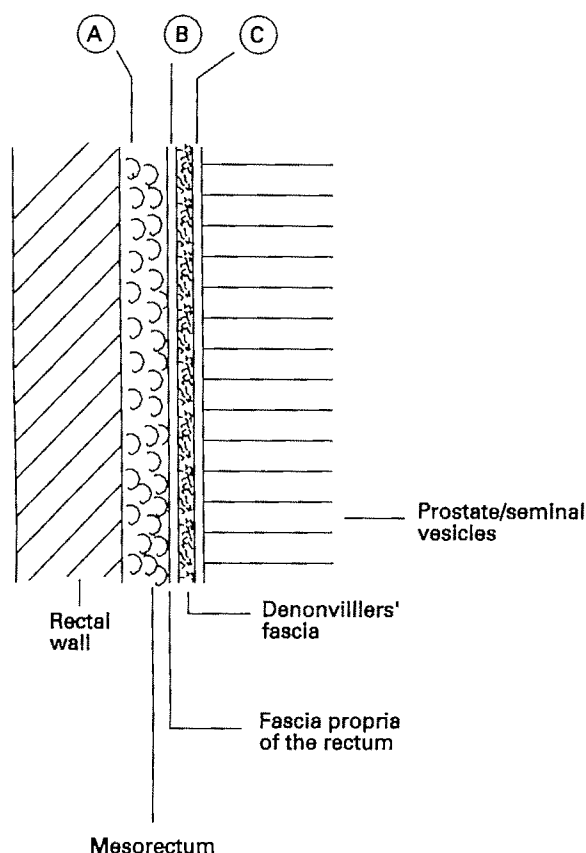


Fig. 2 Schematic diagram of the planes available for anterior rectal dissection. A, close rectal; B, mesorectal; C, extramesorectal

prostate^{15,115}. The mesorectal plane is the appropriate anterior plane for most rectal cancers.

Using mesorectal excision as a starting point, in what circumstances might an extramesorectal dissection lead to better local oncological control? Where the risks of leaving tumour behind anteriorly are high, most surgeons would err on the radical side. Such a situation would occur when the anterior circumferential margin is threatened by the tumour, for example an anterior bulky, fixed or tethered tumour, particularly when extraperitoneal. While the data to support this contention directly are scant, it is a logical approach. It should not, however, be used as an excuse for high sexual dysfunction rates in patients with favourable tumours.

Conversely, might a less radical anterior dissection be used for some tumours without compromising local control? If so, there may be benefits in terms of lower rates of erectile dysfunction. Tumours involving the

anterior quadrant may be more likely to lead to erectile dysfunction than those that do not. Small, posterior tumours are unlikely to impact on the anterior mesorectum, and dissection anteriorly in the mesorectal plane may not be needed; it may be safe to perform an anterior close rectal dissection in such circumstances. The answer to such a question can come only from the generation of good-quality data from appropriately designed studies.

Conclusion

The development and anatomy of Denonvilliers' fascia have been controversial for many years and have led to confusion regarding its operative surgical appearances. Denonvilliers' fascia arises from the fusion of the two walls of the embryological peritoneal cul-de-sac and extends from the deepest point of the rectovesical pouch to the pelvic floor. Histologically it has two distinguishable layers, reflecting its development. However, it is not possible to discern two separate layers macroscopically during pelvic dissection. There is no so-called 'posterior layer' of Denonvilliers' fascia. This terminology has unfortunately persisted and caused both anatomical and surgical misconceptions. The 'posterior layer' is, in fact, the fascia propria of the rectum. Dissection between the 'two layers' of Denonvilliers' fascia is really a dissection between the fascia propria of the rectum, containing the mesorectum, and the true Denonvilliers' fascia covering the prostate and seminal vesicles.

There is no consensus about the relationship of Denonvilliers' fascia to the appropriate plane of anterior dissection for rectal cancer. It is important to appreciate the anatomy of the cavernous nerves. While they may be jeopardized in ensuring a clear anterior margin, the nerves need not be placed at risk unnecessarily in circumstances in which local control should be achieved in any case. The appropriate surgical conduct of anterior dissection should ideally be tailored to the specific surgical situation. Good data to guide us are still awaited.

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Vascular access for haemodialysis

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Background: The recent expansion of renal replacement therapy programmes has been associated with an increase in the number and complexity of patients requiring permanent vascular access. The introduction of strategies designed to maximize secondary access patency is, therefore, increasingly important as a means of prolonging patient survival on dialysis, reducing morbidity and reducing the escalating cost of such programmes.

Methods: A review of the current literature on the planning of vascular access, access surveillance methods and treatment of the most common complications was performed.

Results: Multidisciplinary vascular access planning, increased use of preoperative imaging and the preferential use of autogenous vein are essential to obtain the best long-term results. While vascular access surveillance, in particular protocols involving direct measurement of access flow, enables the prospective detection and treatment of venous stenosis, the precise indications for treating venous stenosis remain unclear. Surgical revision remains the gold standard for the treatment of failing arteriovenous fistulas, but recent advances in interventional radiological techniques along with the suitability of arteriovenous fistulas for percutaneous intervention may offer an effective alternative. The effect of both these interventions on access patency requires comparison in a randomized trial.

Conclusion: The introduction of strategies to improve access patency rates will change vascular access surgical practice away from the construction of new fistulas towards an increase in outpatient percutaneous intervention and surgical revisional procedures. The role of surgical interventions requires clearer definition.

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Introduction

Adequate care of a patient with end-stage renal failure on haemodialysis requires permanent vascular access that delivers a flow rate adequate for the dialysis prescription, has a good long-term patency and is associated with a low complication rate. Currently, the dialysis population is increasing (*Fig. 1.*) owing to a combination of reduced availability of renal transplants, an increase in the number of elderly patients referred for renal replacement therapy and increased patient survival on dialysis. This population increase has been accompanied by a steep rise in haemodialysis access-associated morbidity; vascular access problems now account for a large proportion of renal unit admissions at an ever increasing cost^{1,2}. In the face of this problem, access patency rates have changed little since the Brescia Cimino wrist fistula was first described over 20 years ago^{3–16}. Recent published guidelines from the National Kidney Foundation in the USA¹⁵ have highlighted the lack

of reliable clinical evidence on the prevention and management of haemodialysis access complications, particularly with respect to autogenous vein arteriovenous fistulas (AVFs). The purpose of this review is to highlight recent developments in (1) haemodialysis access planning, (2) the role of fistula surveillance in prolonging fistula patency and (3) improved management of haemodialysis access complications which may improve long-term access function. In particular, the roles of access surveillance programmes and percutaneous interventional techniques need to be better defined in view of their potential impact on surgical practice and case load.

Planning of vascular access

The most important feature of any form of vascular access is its functional length of survival (secondary patency), although complication rates and ease of use are also relevant. General principles involved in access planning

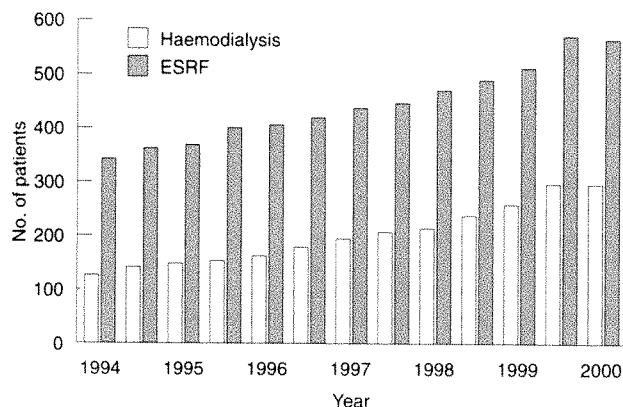


Fig. 1 Increase with time in the number of patients requiring renal replacement therapy at Leicester General Hospital. ESRF, end-stage renal failure

are (1) the use of autogeneous vein where possible, (2) construction of distal AVFs in the arms first, preserving more proximal sites for subsequent procedures, (3) pre-emptive patient education about the need for preservation of the superficial veins of the arm and central veins of the thorax by avoiding venepuncture, and peripheral and central cannulation¹⁷, and (4) fistula construction before the onset of renal replacement therapy as this is associated with both improved access patency and patient survival¹⁸. Proposed methods of improving fistula patency are listed in *Table 1*.

An accurate initial assessment and management plan is particularly relevant. Poor patency rates are associated with increased morbidity and the patency of the primary access, in particular, is important as it is superior to that of all subsequent procedures¹⁶. The best long-term results are produced by good communication between specialties and the fostering of a multidisciplinary approach to access planning. Allon *et al.*¹⁹ report a reduction in the overall cost of the vascular access service, with reduced complication and reoperation rates, following the introduction of a vascular access service coordinator. This person was responsible for acting as a liaison between vascular access surgeons, nephrologists and interventional radiologists, producing regular quality assurance reports, promoting the development of a fistula surveillance programme and allowing the conversion of the majority of vascular access procedures to an outpatient setting. The result was reductions in fistula failure rate, the percentage of patients with temporary vascular access catheters and the overall number of new vascular access procedures performed (from 15 to ten per month). The estimated cost of a new arteriovenous graft fistula fell by 56 per cent¹⁹. Another important consideration is the skill of the operating

Table 1 Methods of improving vascular access patency

Multidisciplinary approach to vascular access planning
Early preoperative surgical assessment and increased use of vascular imaging
Consultant-led service
Pharmacological prevention of intimal hyperplasia
Vascular access surveillance
Prospective treatment of venous occlusive disease

surgeon^{20,21}. Prischl *et al.*²⁰ found that the 3-year patency of wrist fistulas varied from 34 to 62 per cent depending on the surgeon; others²¹ have found a 2-4-fold increased risk of fistula failure when the procedure was performed by unsupervised trainee surgeons.

Preoperative assessment

All patients should initially be referred to a vascular access surgeon for assessment. Characteristics of the arterial, venous and cardiopulmonary systems, along with the patient's life expectancy, influence the type and location of vascular access placement. The adequacy of the superficial veins and arteries in the limbs, as well as the risk of central vein occlusion, can be assessed clinically in most patients²². Published guidelines recommend preoperative imaging of the venous outflow in the presence of any of the risk factors for asymptomatic venous outflow stenosis listed in *Table 2*¹⁵. Venography is the recommended modality for preoperative imaging¹⁵. It is the gold standard for detecting central vein stenosis (*Figure 2*) with higher sensitivity than duplex ultrasonography^{23,24}, although the sensitivity and specificity of the latter is improved if several variables are measured, including vessel compressibility, phasicity of flow with respiration, visualization of thrombus and the presence of spontaneous flow²⁴. Peripheral venous angiography has the major advantage that it provides a road map for the planning of surgical procedures, but this is balanced by several significant limitations. The presence of a distal stenosis prevents venographic assessment of the more proximal vein; venography also gives no indication of the presence of pre-existing intimal hyperplasia or wall thickening. Duplex ultrasonography overcomes some of

Table 2 Recommended indications for preoperative imaging of the arm and central veins¹⁸⁻²⁰

Previous subclavian vein catheterization
Previous ipsilateral upper limb surgery or trauma
Previous ipsilateral failed vascular access
If there is doubt about the adequacy of the superficial veins owing to previous venepuncture or obesity
Transposed brachio basilic arteriovenous fistula is planned ²⁰

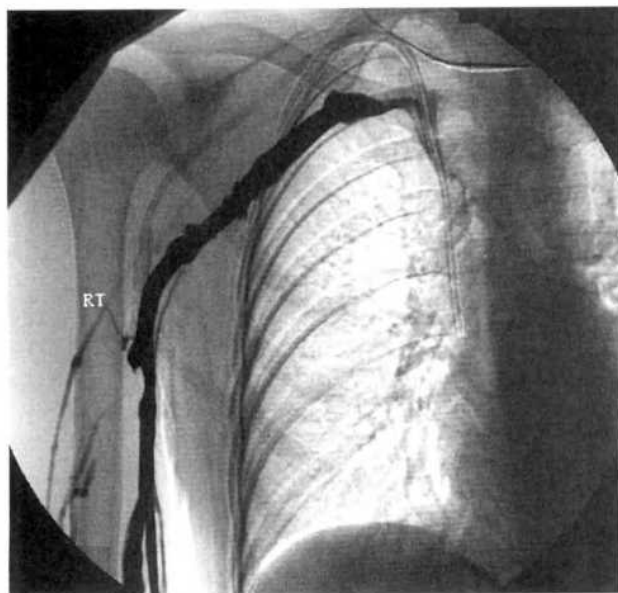


Fig. 2 Venogram demonstrating subclavian vein stenosis. This patient had previously had a temporary dialysis catheter in the right subclavian vein for 8 weeks

these disadvantages and has been used by some to delineate the adequacy of superficial arm veins for peripheral vascular reconstruction with some accuracy^{25,26}. It can also be used to assess arterial inflow in those patients considered at risk of arterial steal²⁷. However, the interpretation of duplex findings are highly operator dependent²⁸ and details of the nature of wall thickening are not always adequate^{26,29}. Magnetic resonance imaging (MRI) and computed tomography have also been used to delineate central and peripheral venous anatomy^{30–32}. MRI is non-invasive and can be used in patients who are sensitized to contrast agents³². However, several studies describe a lower specificity and sensitivity in detecting thromboses of the subclavian and axillary veins^{23,33} and, together with the reduced availability of MRI and the high sensitivity and specificity of alternative imaging modalities, it has not entered widespread clinical use.

Choice of access

The first choice of AVF is the Brescia Cimino radiocephalic arteriovenous fistula³, first described in 1966. It has reported secondary patency rates of 64–72 per cent and 37–72 per cent at 3 and 5 years respectively^{6,8,12,13}. Neither the side-to-side configuration, as described originally³, nor the end-of-vein-to-side-of-artery configuration is superior in terms of overall patency, although the end-to-side technique is associated with a lower incidence of venous

hypertension symptoms in the hand³⁴ and its use is preferred by many surgeons. In the absence of suitable vessels at the wrist, the next choice of AVF is the brachiocephalic or elbow fistula where the cephalic vein or one of its tributaries is anastomosed to the brachial artery at the antecubital fossa^{4,35}. The brachiocephalic AVF has reported patency rates of 50–70 per cent and 34–53 per cent at 3 and 5 years respectively,^{10,36–39}

Both these fistulas can be fashioned under local anaesthesia and they have low complication rates in comparison to other forms of access. They are also resistant to infection compared with constructions using polytetrafluoroethylene (PTFE) grafts. Despite infection rates of 0–6 per cent for wrist fistulas^{11,12} and 8–10 per cent for elbow fistulas^{36,38,39}, the rate of autogenous fistula loss due to infection is low, 0–1 per cent for both types of construction^{6,10–12,36,38}. Infection rates associated with PTFE grafts are higher (8–19 per cent)^{6–8,13}, with graft excision rates of 5–10 per cent attributable to infection alone. Brachiocephalic fistulas are associated with a high incidence of steal (10–20 per cent)^{10,36}. Disadvantages of autogenous AVFs are the long maturation time (up to 4 months for wrist fistulas) and the large proportion of these fistulas (11–30 per cent) that fail before being used for dialysis (primary failure)^{10–13,36}. Attempts to improve the rate of maturation have included hand exercises, with or without a lightly applied tourniquet; there is no evidence to support this.

Some studies have reported higher rates of primary failure, delayed maturation and lower patency in wrist fistulas in diabetic⁴⁰ and elderly⁴¹ patients. This is not the case for brachiocephalic fistulas^{36,42} and, in individual cases, formation of a brachiocephalic fistula as a primary procedure may be preferable. Other studies have reported no difference in outcome in elderly and diabetic patients^{43–44}; an appreciable number of patients with diabetes achieve successful dialysis via radiocephalic fistulas (30–80 per cent)^{40,42}, with no differences in dialysis efficiency between diabetic and non-diabetic patients⁴⁰. The differences appear most marked in the elderly diabetic population and so primary selection of elbow fistulas in such cases may be worthwhile, given the reduced life expectancy of such patients on haemodialysis (50 per cent are dead at 2 years⁴¹).

In the absence of suitable superficial veins in the arm or forearm, the next best type of access is a choice between the insertion of a prosthetic arteriovenous graft and the transposed autologous brachiobasilic AVF⁴⁵. Expanded PTFE was first used as a conduit for vascular access by Volder *et al.*⁵ and has since become the most popular graft material. Biological graft materials, such as long saphenous vein, human umbilical vein and bovine carotid artery, have also been used in the past but they are associated with higher

incidences of infection, rupture, false aneurysm formation and occlusion^{6,46,47}. PTFE has the advantage that it is easy to handle, is always available, can be inserted under local anaesthesia in a wide variety of configurations depending on the available vascular anatomy and, if necessary, can be needled immediately for haemodialysis. The most popular procedures are a loop graft between the brachial artery and the basilic vein, and a straight graft between the radial artery and the basilic vein or between the brachial artery and the axillary vein.

The transposed autologous brachiobasilic AVF is fashioned by mobilizing the basilic vein from its subfascial bed, transposing it to a subcutaneous tunnel on the anterior surface of the arm and anastomosing it to the brachial artery at the level of the antecubital fossa^{35,45}. The procedure is technically feasible in 95–98 per cent of cases^{48,49} owing to the subfascial location of the vein protecting it from previous venepuncture. It has the advantages of resistance to infection as well as requiring only one anastomosis. This latter feature has the double benefit of avoiding the proximal anastomosis associated with outflow stenosis in PTFE grafts and not compromising the insertion of a prosthetic graft at a later date should this become necessary.

The reported secondary patency rates of these alternatives are roughly equal, with 3-year patency rates ranging from 43 to 64 per cent for transposed brachiobasilic fistulas^{37,39,49,50} and 40–59 per cent for PTFE arteriovenous grafts. Despite this equivalence in secondary patency, PTFE grafts are associated with much higher complication rates⁵⁰. Furthermore, the primary patency rate (function up until the first episode of thrombosis or failure to provide adequate dialysis) for brachiobasilic fistulas is superior to that of PTFE grafts which require up to 1.4 further procedures per year to maintain patency⁷. Secondary patency rates of PTFE grafts have improved with the introduction of graft surveillance and refinements in both percutaneous techniques and surgical revision; some modern series of PTFE grafts report secondary patency rates as high as 87 per cent at 3 years¹⁴. In general, however, large centres with active prospective surveillance programmes have secondary patency rates for PTFE grafts of approximately 50 per cent at 3 years and this is achieved at the expense of a threefold to sixfold increase in the number of procedures over that required to maintain patency of native vein fistulas⁵¹.

When both the non-dominant and dominant arm vessels are exhausted, remaining options for long-term access are leg or thigh grafts or grafts involving the subclavian or axillary vessels. The patency rate of PTFE thigh grafts is approximately 50 per cent at 2 years⁵². Graft infection is a particular risk in the groin, and is associated with anastomotic dehiscence, haemorrhage and death. The

incidence of infection in groin PTFE grafts ranges from 16 to 35 per cent^{52,53}, and other reports of mixed PTFE and biological arteriovenous thigh grafts describe a leg amputation rate of 22 per cent and a mortality rate of 18 per cent attributable to infection⁵⁴. Another complicating factor is the high incidence of peripheral vascular disease in renal patients with resulting high rates of steal (16 per cent) and subsequent leg amputation (7 per cent)⁷. Because of these risks, the insertion of leg grafts should be seen as a last resort in those for whom all other options for long-term access have been exhausted.

On the other hand, several specialist centres report good long-term secondary patency with grafts from the axillary artery below the clavicle to the contralateral axillary vein or internal jugular vein⁵⁵. The graft is tunnelled subcutaneously on the anterior chest wall, facilitating easy venepuncture. In experienced hands 2-year patency rates reach 77 per cent, with infection rates similar to those for conventional upper limb PTFE grafts⁵⁶. Cuffed tunnelled catheters are also an option for long-term access in patients without suitable alternatives. Their widespread use cannot be recommended, however, owing to high rates of catheter thrombosis (25–40 per cent)^{57–59}, sepsis (2–18 per cent)^{58–60} and associated central vein thrombosis (30 per cent)⁶¹.

Venous occlusive disease

Over 60 per cent of AVFs and 80 per cent of PTFE grafts fail because of thrombosis caused by a stenosis in the venous circulation⁶². These stenoses are characterized histologically by neointimal hyperplasia^{63,64}, a pathological response of vascular tissue to injury⁶⁵. Stenosis in an autogenous AVF occurs predominantly within 2–3 cm of the arteriovenous anastomosis, or at needling sites and calcified venous valves⁶⁶ (Figure 3), while 50–70 per cent of venous stenoses associated with PTFE grafts occur within 3 cm of the vein-to-graft anastomosis^{67,68}. Central venous stenosis, typically subclavian vein stenosis, accounts for roughly 20 and 40 per cent of venous stenoses associated with arteriovenous PTFE grafts and AVFs respectively^{66,69}; it is associated with central venous cannulation. The differences in the incidence and distribution of venous stenosis related to AVFs and arteriovenous grafts are due largely to an accelerated rate of stenosis at the graft-to-vein anastomosis associated with PTFE grafts⁵¹. They reflect different aetiological factors in each type of fistula. In autogenous AVFs these include a non-denuding stretching injury produced by blood flow at arterial pressure, and endothelial trauma from repeated venepuncture with a subsequent release of mitogens from the activated platelet plug required to stop bleeding⁷⁰. With PTFE grafts the accelerated

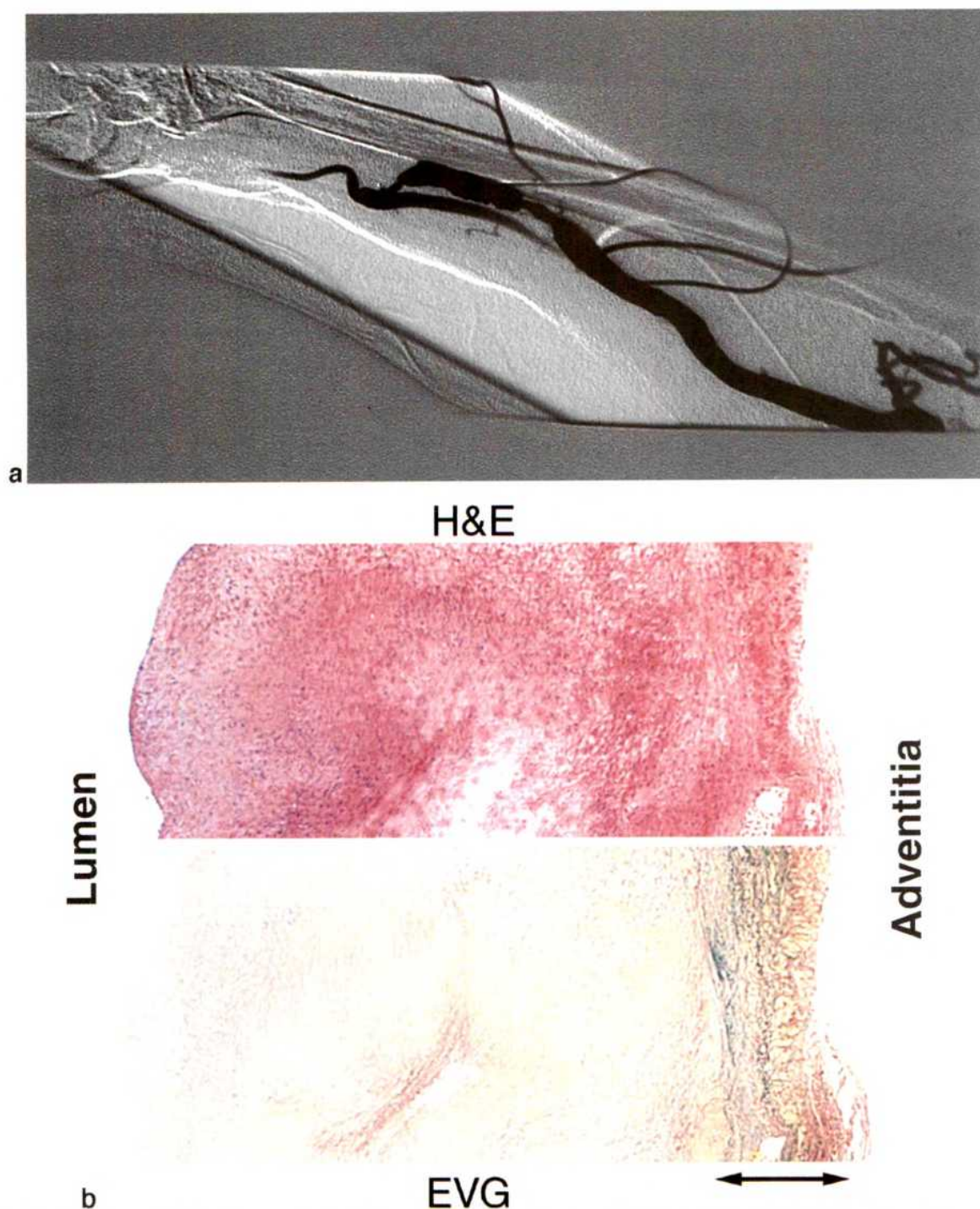


Fig. 3 **a** Right radiocephalic fistulogram demonstrating a postanastomotic stenosis and a more proximal needle-site stenosis.
b Photomicrographs ($\times 40$ magnification) of a section of an excised needle-site stenosis from an autogeneous vein fistula demonstrating the cellular neointima (haematoxylin and eosin stain, H&E), with the original vein wall thickness demonstrated by elastin staining of the media (elastin van Gieson, EVG) (arrowed). (Images reproduced courtesy of Dr P. N. Furness, Department of Pathology, Leicester General Hospital)

intimal hyperplasia found in proximity to the arteriovenous anastomosis is due to a combination of flow turbulence,

surgical trauma, compliance mismatch between vein and graft⁷¹, and the release of growth factors from fibrin and

platelets that accumulate on the luminal surface⁷². As all of these aetiological factors are prerequisite to access function or inherent in the insertion of prosthetic material, it is difficult to see how they may be prevented. Attempts to address some of these problems through increased graft compliance⁷³ and reduced thrombogenicity⁷²⁻⁷⁶ are largely experimental and have produced mixed results. The wider use of pharmacological agents to reduce intimal hyperplasia seems warranted but there are few reported trials of such agents in the haemodialysis vascular access context. One such agent, dipyridole, has been shown to improve the long-term patency of PTFE vascular grafts while aspirin does not⁷⁷.

Vascular access surveillance

Early detection and correction of haemodynamically significant stenoses in AVFs and arteriovenous grafts should theoretically reduce thrombosis rates and this has been demonstrated in several non-randomized clinical studies. Intervention with percutaneous transluminal angioplasty (PTA) or surgical revision to correct stenosis reduces the rate of AVF and arteriovenous graft thrombosis⁷⁸⁻⁸². The pre-emption of thrombosis should have the additional economic impact of reducing emergency admissions due to access thrombosis, reducing the need for temporary access catheters with their attendant complications, and preventing underdialysis with its associated morbidity and mortality rates¹⁸. Although the benefits of access surveillance appear obvious, the best means of detecting the development of stenosis is unclear. This is complicated by the different haemodynamics in AVFs and arteriovenous grafts; not all tests are suitable for both.

Pressure-flow characteristics of autogeneous arteriovenous fistulas

After construction, native AVFs show a slow increase in access blood flow over several months after which flow remains fairly constant⁸³⁻⁸⁶. Flow rates for AVFs vary considerably from individual to individual (1000 ml/min is not uncommon) and, in general, the pressure drop in the AVF is low owing to the low resistance produced by abundant venous collaterals. The degree of collateral flow is usually such that when a stenosis develops in an AVF a major increase in intra-access pressure is prevented as long as the collaterals remain open⁸⁶. Exceptions to this are a stenosis within the axillary or subclavian vein, where collateral flow is less, and pressure increases in the fistula causing reduced flow, and a stenosis in a transposed brachio basilic vein AVF where the isolated vein segment behaves more like an arterial graft. Measuring pressure within an autogeneous

vein fistula is, therefore, an insensitive method of detecting vein stenosis. Thrombosis occurs in an AVF at blood flows of less than 200 ml/min⁸⁶ and access blood flow is the best predictive measurement of impending AVF thrombosis.

Pressure-flow characteristics of arteriovenous grafts

After construction of an arteriovenous graft fistula, blood flow rapidly increases to a maximum over several weeks after which it declines steadily owing to the development of a progressive stenosis at the vein-to-graft anastomosis^{87,88}. The absolute flow in an arteriovenous graft is limited by the diameter of the graft at its distal anastomosis or the diameter of the adjacent draining vein. Stenosis occurs preferentially in this segment, where there is no collateral flow. An increase in the resistance of the draining segment due to stenosis is associated with a reciprocal drop in flow. Serial measurements of intra-access pressure can, therefore, provide an indication of the development of venous stenosis. Arteriovenous grafts begin to thrombose at flow rates of less than 600 ml/min⁸⁶, well above the flow rate required to provide adequate dialysis (about 300 ml/min). Clinical and physiological measurements of inadequate dialysis are, therefore, insensitive at detecting stenosis in arteriovenous grafts.

Effective surveillance of both grafts and arteriovenous fistulas requires the design of protocols in which clinical variables and measurements of access function are collated. Important considerations of any surveillance measurement are that it should be sensitive and specific, and should be able to detect stenosis at an early stage. It should be inexpensive, reproducible and be able to be repeated frequently enough to detect the development of stenosis before thrombosis occurs. Different rates of stenosis development in PTFE grafts and native AVFs means that different surveillance protocols may be required for each type of fistula.

Clinical findings in failing access

Regular inspection of the access for clinical evidence of dysfunction is an essential part of any surveillance programme, although clinical surveillance in isolation is inadequate⁸⁸. It is recommended that such surveillance is performed at least once per week. In the case of an AVF, evidence of underlying central vein stenosis includes arm swelling, prolonged bleeding and a previous history of subclavian vein cannulation. Indicators of poor flow are difficulty with needling or recurrent episodes of needle thrombosis; the conversion of a palpable thrill to a pulsation in a fistula suggests a proximal stenosis⁸⁸. Similar clinical findings are found in failing arteriovenous grafts. In

particular, the presence of a thrill over such a graft is consistent with flow above 450 ml/min while a palpable pulse over the graft is associated with flow below this level⁸⁸. A high-pitched bruit on auscultation at the distal anastomosis may indicate an underlying stenosis.

Techniques for measuring access flow

Measuring access flow is the most sensitive method of predicting impending thrombosis in both AVFs and arteriovenous grafts, and is likely to become the standard measurement of function. The major disadvantages of the available techniques are that they require much time and effort, and are expensive. Several direct methods of measuring flow while patients are being dialysed are available. The most well studied of these⁸⁶ involves the injection of a saline bolus through the venous line with the arterial and venous needle positions reversed (arterial needle proximal). This can be achieved by reversing dialyser flow during dialysis. The dilution of the blood in the arterial and venous lines is detected by ultrasound sensors in the dialyser lines, and the difference in dilution is used to calculate fistula flow. Sequential reduction in flow reliably predicts arteriovenous stenosis and its use in predicting thrombosis in AVFs and arteriovenous grafts has been validated in several prospective trials^{89,90}. Bosman *et al.*⁸⁹ reported a highly significant increase in rate of thrombosis (risk ratio 7.2, $P < 0.001$) in arteriovenous grafts with flow less than 600 ml/min, while Neyra *et al.*⁹⁰ reported a significantly increased risk (13.6-fold) of thrombosis in grafts and AVFs with a 15 per cent reduction in flow over two consecutive measurements.

Duplex ultrasonography may also be used to calculate fistula flow as well as to delineate and measure stenosis, although its usefulness is limited by the need to measure flow velocity and lumen diameter accurately. Flow velocity is difficult to measure in AVFs and arteriovenous grafts because of turbulence, and the measurement of lumen diameter is prone to observer error. Furthermore, variation in calibration between machines produces differing values of fistula flow. In spite of these disadvantages, duplex ultrasonography seems a reliable predictor of access stenosis in both AVFs and arteriovenous grafts⁸⁸. Trerotola *et al.*⁸⁸ measured brachial artery flow as an index of access flow at intervals of 3–6 months, and demonstrated a positive correlation between Doppler signal frequency and subsequent thrombosis. The major limiting factor is the time and expense required to perform sequential studies on every access frequently enough to improve patency rates. Similar reasons also limit the introduction of magnetic resonance techniques for measuring flow²⁹.

Techniques for calculating access pressure

Intra-access pressure is a useful indirect measurement of intra-access flow in arteriovenous grafts. The underlying principle is measurement of the pressure in the venous drip chamber either with the dialyser flowing (dynamic) or with no flow in the dialyser (static). Dynamic pressure measurements are raised falsely by the pressure rise produced by the resistance of the dialyser tubing and needle, and this method requires a standard protocol outlining needle and tubing type, needle position and pump pressure to provide reproducible measurements. Dynamic venous drip chamber pressures when measured sequentially have been used to detect graft stenosis for many years⁹¹. The method is cheap, can be performed during dialysis and, combined with clinical examination, is 81 per cent sensitive and 85 per cent specific at detecting venous stenosis in arteriovenous grafts⁹². It is, however, less sensitive than flow measurements⁸⁹ and may yield a wide variation of reading depending on needle site and position. Many of these problems can be overcome by the measurement of static pressure⁹³. The pressure in the venous drip chamber is an accurate indicator of intra-access pressure in the absence of dialyser flow after calculating the effect of the height of the drip chamber. The ratio of this measurement relative to the mean blood pressure is more sensitive than dynamic pressure measurement for predicting access stenosis if measured sequentially (93 *versus* 36 per cent)⁹³. While such measurements require additional time and are prone to calculation error, they do offer a reasonably accurate method of detecting graft stenosis.

Techniques for measuring access recirculation

Access recirculation refers to the retrograde flow that occurs between the arterial and venous dialyser needles when the dialyser pump speed is higher than the fistula flow⁹⁴. It is, therefore, an indirect measurement of access flow and is useful in detecting access dysfunction in AVFs, but not in arteriovenous grafts. This is because the flow rate predictive of thrombosis in arteriovenous grafts is higher than normal dialyser flow. The chemical effect of recirculation is to dilute the venous line blood with blood already cleared of solute, thereby reducing the adequacy of dialysis. Recirculation should occur in an AVF at flows of 300–500 ml/min and may be detected by comparing solute concentration in the arterial blood entering the fistula with the concentrations in the arterial and venous dialyser lines. Recirculation can be calculated by measuring the urea concentration in each of these blood samples, and has the advantages of being reproducible, inexpensive and correlat-

ing well with low AVF flow⁹⁵. This is offset by the margin of error associated with multiple measurements and the fact that all blood urea calculations are prone to variation of up to 10 per cent depending on laboratory technique. In addition, measurement of arterial blood urea concentration presents a practical problem. Peripheral venous blood is not an accurate representation of arterial blood although one method of reducing error is to reduce dialyser blood flow to a flow rate at which recirculation is unlikely (120 ml/min) and use a second sample from the arterial line as a measurement of the blood entering the access⁹⁵. This sample must be taken at exactly 10 s after flow has been decreased to reduce further error. Another potential problem is the presence of a stenosis between the needles producing lower recirculation measurements in the presence of low flow.

Various non-urea-based alternatives of calculating recirculation have been developed, one of which involves the injection of a saline bolus into the venous line and measuring alterations in blood dilution between the arterial and venous lines by ultrasonography or temperature monitoring (similar to direct flow measurements)⁹⁶. Although more accurate, this requires specialist equipment and is more time consuming. Published guidelines suggest the further investigation of recirculation above 10 per cent for urea-based and above 5 per cent for non-urea-based measurements¹⁵. Complete reversal of dialyser flow produces recirculation measurements of 20 per cent while the standards set for investigation represent the window between the margins of error of the two different forms of measurement and the value for complete recirculation. Prospective evaluation of the urea-based technique has produced poor results at predicting thrombotic episodes⁹⁷⁻⁹⁹. The number of AVFs in these studies was low, however, and the use of this technique in a large study of autogenous fistulas is awaited. The use of thermodilution techniques has met with better success¹⁰⁰, with a reported efficacy equivalent to that of access flow methods.

Intervention

The endpoint of all access surveillance is referral for fistulography, followed by either surgical revision or PTA of the affected segment to restore normal flow. An important feature of any subsequent intervention should be that it restores the measured value to the normal range, thereby permitting ongoing surveillance. Currently, the precise indications for intervention and the appropriate method of intervention remain unclear. The quality of imaging is important and venography remains the gold standard in this regard¹⁰¹⁻¹⁰³. Duplex

ultrasonography can be a useful tool for delineating lesions such as extramural haematoma, aneurysm and mural thrombus, and can be used to supplement venography. For a fistulogram to be considered adequate, it must visualize the anastomosis, draining veins and central veins, as occult central vein stenosis is a common cause of access dysfunction. In general, greater than 50 per cent stenosis of the vessel luminal diameter on uniplanar angiography has been considered to be haemodynamically significant and to require treatment⁵¹. However, in a recent randomized controlled trial, Lumsden *et al.*¹⁰⁴ were unable to show any improvement in arteriovenous graft patency at 12 months' follow-up when patients with angiographic evidence of at least 50 per cent stenosis were randomized to PTA or observation. Access flow was not measured in this trial, however, and functional measurements may better define those accesses requiring intervention.

Treatment of venous stenosis

The correct management of venous stenosis can prolong secondary patency. This is more noticeable in the case of grafts than native fistulas⁵¹, largely because of the accelerated rate of stenosis and higher rate of thrombosis in the former. The role of intervention in native AVFs is less well established. Oakes *et al.*¹⁰⁵ report primary patency after treatment of distal stenosis in wrist fistulas by a more proximal revision in the forearm as 57 per cent at 1 year. Similarly, 1-year primary patency is 50 per cent after surgical revision of distal stenosis in autogenous elbow fistulas (G. Murphy and M. L. Nicholson, unpublished observations). In the latter group, 50 per cent of revisions required the insertion of a short bridge graft to bypass the stenotic segment. Reports of primary patency after PTA of stenosis in native AVFs (*Figure 4*) vary widely (16-44 per cent 1-year primary patency)^{78,81,82}, with the best results of 62 per cent 1-year primary patency following PTA of juxta-anastomotic venous stenosis in wrist fistulas⁸¹. To date, no prospective trial comparing PTA and operation has been performed.

Surgical revision of venous stenosis in arteriovenous grafts results in better intervention-free survival than PTA. Brooks *et al.*¹⁰⁶ reported superior 1-year primary and secondary patency rates for patch angioplasty or local revision than for PTA in a randomized controlled trial. In addition, surgical revision was less costly. These advantages are offset by the progressive loss of available vein for reconstruction (venous capital) associated with surgical revisions. The major disadvantage of all percutaneous techniques is that balloon angioplasty itself is a major stimulus for intimal hyperplasia; restenosis is

common and frequent re-evaluation of fistulas is essential after PTA. Approximately 50 per cent of stenoses in AVFs and 25 per cent in arteriovenous grafts recur within

6 months⁸¹, requiring repeated angioplasty to maintain patency. Furthermore, the period between interventions appears to decrease after each balloon angioplasty and



Fig. 4 **a** Fistulography performed because of difficulty with venepuncture of a left brachiocephalic fistula reveals a long stenosis at the needling site. **b** The stenosis is corrected by balloon angioplasty, but some extravasation of contrast agent is noted. This is controlled by the introduction of a covered stent. (Images courtesy of Dr K. Blanchard, Department of Radiology, Leicester General Hospital)

surgical revision of any rapidly recurrent stenosis may be more effective¹⁰⁷. The insertion of prosthetic stents in an attempt to improve the results of PTA has shown no overall benefit^{74,108}, except for elastic stenoses¹⁰⁹. Stents also prevent further surgical reconstruction of the affected segment and so one of the major advantages of percutaneous techniques, preservation of venous capital, is lost. Overall, PTA alone has worse results in long, elastic, recurrent stenoses or critical stenoses (more than 90 per cent)^{51,81,109}, and surgery or PTA plus stenting is likely to be superior in such circumstances.

Central vein stenoses present a separate problem for which stents may be beneficial. PTA of these lesions has a poor long-term success rate and a higher proportion of these stenoses tend to have elastic recoil^{109,110}. Reported patency after PTA ranges from 23 to 29 per cent at 6 months. Stenting of such lesions is associated with improved patency; Vesely *et al.*¹¹¹ and Gray *et al.*¹¹² have reported 1-year primary patency rates of 22 and 20 per cent respectively after stent insertion in elastic lesions.

Management of complications

The majority of late failures of AVFs and arteriovenous grafts is caused by the development of thrombosis and poor flow secondary to venous stenosis. Another significant cause of access failure, particularly in arteriovenous grafts, is infection. Other complications include arterial steal, arm oedema and venous hypertension secondary to proximal vein stenosis and occlusion, bleeding, and aneurysm and pseudoaneurysm development. As thrombosis, infection and steal together represent a large proportion of access complications they will be considered here.

Thrombosis

Thrombosis accounts for the failure of up to 80 per cent of haemodialysis access^{51,62}. It is important to detect and treat any identifiable cause of thrombosis at the time of thrombectomy or shortly afterwards, as failure to do so is associated with rapid early rethrombosis^{8,13}. Twenty per cent of thrombosis occurs in the absence of any identifiable stenosis; other potential causes are hypotension or fluid depletion during dialysis, compression during sleep or from adjacent haematoma after venepuncture, and excessive fistula compression after dialysis.

The type of access and the site of thrombosis are important determinants of treatment outcome. Thrombosis of native AVFs, if noted early, may be salvaged surgically as clot propagation is usually limited by residual flow in venous collaterals; however, extensive clot in a native

fistula due to proximal stenosis is often difficult to treat. Kherlaikian *et al.*⁸ reported a salvage rate of 25 per cent for thrombosed wrist fistulas, and Palder *et al.*¹³ reported a secondary patency rate in wrist fistulas that had undergone embolectomy and proximal revision equivalent to that of those that had not failed. Romero *et al.*¹¹³ reported the best results for thrombosis secondary to distal stenotic lesions in wrist AVFs when the fistula could be salvaged by a more proximal revision in the forearm (50 per cent patency at 2 years). Experience of percutaneous treatment of thrombosed native AVFs is limited, but initial reports are favourable. In a small series, Vorwerk *et al.*¹¹⁴ reported 95 per cent success at restoring patency in 21 wrist fistulas. In a second report¹¹⁵ these authors described superior patency with pulse spray mechanical thrombolysis and angioplasty in thrombosed wrist fistulas than in a parallel series of thrombosed arteriovenous grafts. The apparent superiority of modern percutaneous techniques in the management of thrombosed native fistulas is important; a prospective comparison of surgical *versus* percutaneous management of thrombosed AVFs has not yet been reported.

The salvage of thrombosed arteriovenous grafts has received much more attention, with better results generally than for thrombosed native AVFs. Largely equivalent results are described for percutaneous thrombolysis and surgical thrombectomy, with approximately 90 per cent successful restoration of graft flow using either treatment⁵¹. Percutaneous techniques have undergone major developments in recent years, including pharmacological methods in which a fibrinolytic agent is infused directly into the clot^{116,117} and mechanical methods such as balloon thrombectomy¹¹⁸, pulse spray clot maceration with saline¹¹⁹, thromboaspiration or clot maceration using mechanical devices^{120,121}. Pulse spray clot maceration or hydrodynamic thrombectomy¹¹⁹ involves a catheter or catheters with multiple side slits being inserted into the clotted graft, and the clot macerated by jets of saline from the side holes (*Fig. 5*). The injection of urokinase through the side holes, also known as pharmacomechanical thrombolysis, has similar efficacy but has the disadvantage of a potential increase in haemorrhagic complications¹¹⁹. Overall, the success rates of percutaneous strategies are broadly similar, with approximately 90 per cent success at restoring graft patency^{118–121}. The major complication of mechanical thrombolysis is embolization to the lungs or distal arterial circulation. Swan *et al.*¹²¹ reported lung perfusion defects in 25 of 43 patients following pharmacomechanical thrombolysis, of whom two died. Arterial emboli tend to be less common (1–2 per cent) and, when symptomatic, are usually amenable to treatment¹²². Pharmacological thrombolysis on its own is less effective

(60–70 per cent success)^{116,117} with additional haemorrhagic side-effects; its use is decreasing.

The choice between surgical or percutaneous thrombectomy generally rests with the technologies available in each individual centre. Surgical treatment does not require the technological support required for mechanical thrombolysis, and surgical revision patch angioplasty or bypass of the recanalized segment can be performed simultaneously. Modern percutaneous techniques require the services of an interventional vascular laboratory at short notice but permit angioplasty of stenotic lesions, thereby preserving venous capital. Large retrospective studies have suggested better long-term patency following mechanical thrombolysis and angioplasty¹²³, but two randomized trials comparing surgical *versus* mechanical thrombectomy both showed superior success rates with surgery and revision (94 and 83 per cent respectively)^{124,125}, although the success rate for mechanical thrombolysis was low in both trials (72 and 67 per cent respectively). Marston *et al.*¹²⁵ reported better primary patency with surgical thrombectomy and revision

(25 *versus* 9 per cent) at 12 months and this was associated with reduced cost.

Infection

Access-related infection accounts for the failure of up to 20 per cent of arteriovenous grafts, as well as a much smaller proportion of native fistulas⁶⁸. Prophylactic antibiotics are recommended for the insertion of prosthetic grafts, and preoperative reduction in levels of skin colonization with *Staphylococcus aureus* (70 per cent in uraemic patients compared with 10 per cent in the general population) has also been shown to reduce the incidence of access-related sepsis¹²⁶. Wound infection in the postoperative period after arteriovenous graft construction and AVF formation alike poses a high risk of wound dehiscence and secondary haemorrhage. Such cases require treatment with intravenous antibiotics and drainage of collections of pus. The organisms responsible are predominantly coagulase-negative and -positive staphylococci¹²⁷, although the proportion

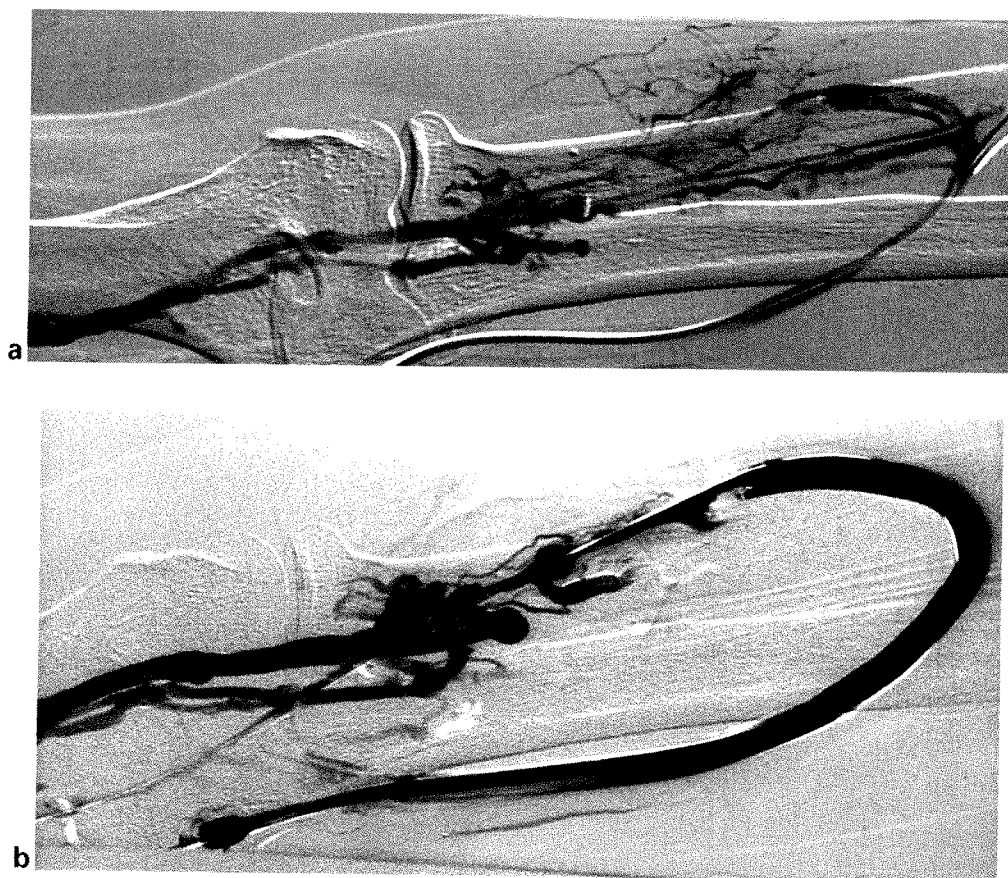


Fig. 5 **a** Mechanical thrombolysis pulse spray catheter is inserted into a thrombosed left forearm brachio basilic polytetrafluoroethylene loop graft. **b** Hydrodynamic thrombectomy reveals a long venous stenosis proximal to the graft-to-vein anastomosis. This required surgical revision. (Images courtesy of Dr K. Blanchard, Department of Radiology, Leicester General Hospital)

of Gram-negative infections is increasing. Later infections of autogenous fistulas often occur at needle sites but, although severe complications can occur and require fistula ligation, most are uncomplicated and resolve with simple antibiotic therapy^{8,128}. PTFE graft usage in preference to autogenous AVF is associated with a fivefold increase in access infection¹²⁹ and few series report good results with simple antibiotic therapy^{13,130,131}. Untreated graft infection is associated with bacteraemia, septic emboli, secondary haemorrhage and death¹²⁷. A collection around a synthetic graft with associated bacteraemia requires graft excision and intravenous antibiotics, although if the infection/collection is localized 50–60 per cent of grafts may be salvaged by limited excision and bypass of the infected segment^{9,130,131}. One exception is newly inserted grafts; when the graft has yet to be incorporated into the surrounding tissue the recommended treatment is graft excision, regardless of the apparent extent of the infection.

Steal

Vascular steal, in which a sufficient proportion of the arterial flow is shunted back towards the heart such that the distal limb becomes ischaemic, is a feature of lower limb arteriovenous grafts and, to a lesser extent, brachial artery fistulas^{10,36,52}. Risk factors for arterial steal are diabetes and pre-existing vascular disease. Clinically, the patient presents with classical signs of distal limb ischaemia that develop gradually in the weeks after fistula construction or, occasionally, as acute nerve ischaemia in the postoperative period. In the latter case treatment is emergency ligation of the fistula, although if nerve infarction has occurred the neural deficit will be permanent. In other circumstances, steal can usually be investigated by either an arch angiogram to delineate proximal lesions amenable to PTA, or by duplex ultrasonography of the anastomoses to exclude stenosis. In a proportion of patients symptoms improve without treatment but if they persist treatment options include banding or plication of the fistula, with intraoperative flow monitoring to assess the required degree of luminal narrowing¹³². It may also be possible to ligate the artery distal to the fistula anastomosis and insert a jump graft from a site proximal to the anastomosis to the distal arm. Successful restoration of function has been reported in over 90 per cent of patients using this latter technique^{133,134}. If such interventions are unsuccessful, ligation of the fistula is required.

Conclusion

The recent expansion of renal replacement therapy programmes has been associated with an increase in the

number, age and complexity of patients presenting to the surgeon for vascular access surgery. The introduction of strategies designed to maximize secondary access patency is, therefore, increasingly important as a means of prolonging patient survival on dialysis, reducing morbidity and reducing costs. Such strategies include multidisciplinary access planning, increased use of preoperative imaging, and a reduction in the use of temporary dialysis catheters in the subclavian vein. A major objective over the coming years should be the widespread introduction of fistula surveillance. There is no overall agreement about the most suitable test and the development of the optimal protocol for access surveillance is some way off. This is complicated by the difference in efficacy of various tests with respect to grafts and native AVFs, the cost and availability of different technologies, and the difference in the natural history of stenosis between the two forms of access. Direct measurement of access blood flow appears to hold the most promise as the best form of monitoring, although the cost of equipment and personnel required is high. In terms of surgical case load, the introduction of access surveillance should result in a trend away from the construction of new accesses towards outpatient percutaneous intervention and an increase in revisional procedures. Randomized trials of these treatment options are now required, particularly for native AVFs.

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Factors predictive of outcome after surgery for faecal incontinence

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Background: Surgical treatment of faecal incontinence may be categorized into procedures that either repair or augment the native sphincter mechanism or, alternatively, require construction of a neosphincter using either autologous tissue or an artificial device.

Methods: This article reviews the currently available surgical options for the treatment of faecal incontinence, discusses factors predictive of outcome, and includes an algorithm for treatment.

Results and conclusion: Procedures such as postanal repair, direct sphincter repair and reefing are seldom used. Overlapping repair has become the operation of choice in incontinent patients with isolated anterior defects in the external anal sphincter muscle, particularly in postobstetric trauma. Pudendal neuropathy seems to be a predictive factor of success, although this is not universally accepted. Total pelvic floor repair has been offered as a recent alternative. Neosphincter procedures include a gluteoplasty, non-stimulated and stimulated unilateral or bilateral graciloplasty and artificial bowel sphincter. The success and morbidity rates with the stimulated graciloplasty and artificial bowel sphincter appear similar. The newest alternative, sacral nerve stimulation, seems promising. In the final analysis, case selection and surgical judgement are probably the most important factors influencing the success of surgery for faecal incontinence.

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Introduction

Anal incontinence can be defined as the loss of anal sphincter control and the consequent inability to defer the call to stool to a socially acceptable time and place. The result may be either unawareness of or inability to prevent the unwanted release of gas, or liquid or solid stool. Daily or weekly episodes occur in about 2 per cent of the adult population and in about 7 per cent of healthy independent adults over the age of 65 years^{1–3}. The disorder causes great personal disability and has a high financial cost, as attested to by the fact that in the USA more than US \$400 million each year is spent on faecal incontinence appliances alone, and faecal incontinence is the second most common reason (more common than dementia) for requesting placement in a nursing home⁴. Among patients who are institutionalized, the prevalence may be as high as 25 per cent; one-third of elderly people in retirement homes or hospitals are incontinent to stool^{5,6}.

Anal continence requires both intact sensation and motor innervation, and an anatomically intact sphincteric

complex⁷. Although pudendal nerve damage plays an important role in the pathophysiology of faecal incontinence^{7–9}, the majority of women who complain of such incontinence have anatomical defects in the external anal sphincter^{10–13}. The most common cause of this damage to the sphincter muscles is vaginal delivery^{8,9}. Overt sphincter rupture occurs during 5 per cent of vaginal deliveries but this increases to as high as 50 per cent with the use of midline episiotomy and/or operative vaginal delivery^{10,14}. Not surprisingly, incontinence of flatus or stool develops in 3–44 per cent of women following vaginal delivery^{7,14–17}. Donnelly *et al.*¹⁸, in a study of 208 women, reported postpartum incidences of urgency of 10 per cent, incontinence of flatus of 13 per cent, and incontinence of stool of 10 per cent. The mean resting anal pressure fell from 56 to 43 mmHg and the mean squeeze pressure fell from 52 to 32 mmHg.

Diagnosis

A number of incontinence scoring systems have been proposed to assist clinical decision making and post-

therapeutic assessment of results^{19–22}, one of which acknowledges the important contribution of symptom severity to quality of life²³ (Table 1). Shelton and Madoff³² recently reviewed many of the frequently used systems but the mere fact that at least 12 such systems exist reveals the lack of uniform acceptance of any one method. Evaluation of anorectal symptoms may rely on history, physical examination, manometry and concentric needle electromyographic techniques^{7,8,10,12,33}. Recently, anal endosonography has been used to visualize both the internal and external anal sphincters^{10–13,33–37}. In addition, magnetic resonance imaging (MRI) has also been proposed for assessment of the anal sphincter complex. Schafer *et al.*³⁸ found that MRI had a much lower resolution that caused difficulty in differentiation between internal and external sphincters, making it inferior to ultrasonography.

Surgical treatment (excluding neosphincter procedures)

Postanal repair

Because of the theoretical importance of an adequate anorectal angle in the maintenance of continence, Sir Alan

Parks *et al.*³⁹ devised an operation to restore this angle in incontinent patients. Posterior levatorplasty was thought to improve continence both by making the anorectal angle more acute and by lengthening the anal canal. Parks achieved the best results for this technique in his first series³⁹; more recent outcomes included success in between 32 and 87 per cent of cases (Table 2). Bartolo *et al.*⁴⁷ demonstrated that the change in the anorectal angle did not alter final results, while Womack *et al.*²¹ found that the restoration of continence depended on the ability to close the anal canal adequately. Hill *et al.*⁴⁸ noted that pudendal neuropathy was not a direct consequence of postanal repair as pudendal latency also increases in untreated patients. In a long-term analysis of postanal repair for patients with idiopathic incontinence, Setti Carraro *et al.*⁴⁹ concluded that this operation was successful in relieving faecal incontinence at 5–8 years in only 33 per cent of patients while in another 33 per cent an improvement in the frequency of incontinent episodes may be achieved. In addition, they reported that pudendal neuropathy was the only predictor of adverse outcome after postanal repair.

Patients with no demonstrable sphincter defect and poor resting pressures, and who have either failed or do not wish to undergo biofeedback therapy, are potential candidates. Similarly, those in whom an overlapping sphincter repair has achieved anatomical but not functional success can occasionally be offered a postanal repair. Using these criteria, between 1991 and 1997 Mavrantonis *et al.*⁴⁶ performed 20 postanal repairs without faecal diversion on 20 women of mean age 67 (range 40–80) years. Physiological evaluation was performed in all patients; the morbidity rate was 5 per cent with no deaths at mean follow-up of 22.3 months. The success rate was 35 per cent, with an improvement in the mean continence score from 16.7 to 2.6 at a follow-up of 22.3 months in the seven patients in whom success was achieved. Neither clinical nor physiological variables were predictors of success. Although the success rate of this operation is poor, it is relatively free of morbidity

Table 1 Faecal incontinence scoring systems

Reference	Year	Scores
Womack <i>et al.</i> ²¹	1988	A–D
Holschneider ²⁴	1983	0–14 (0, worst; 14, best)
Rothenberger ²⁵	1989	0–30
Pescatori <i>et al.</i> ¹⁹	1992	0–9
Luniss <i>et al.</i> ²⁶	1994	0–13
Jorge and Wexner ²³	1993	0–20
Parks ²²	1975	1–4
Rainey <i>et al.</i> ²⁷	1990	A–C
Kelly ²⁸	1969	0–6
Broden <i>et al.</i> ²⁹	1988	1–3
Corman ³⁰	1985	Excellent, Good, Fair, Poor
Rudd ³¹	1979	I–V

Table 2 Results of postanal repair

Reference	Year	No. of patients	Results (%)		
			Excellent/good	Fair	Poor
Keighley and Fielding ²⁰	1983	56*	67*	–	–
Browning and Parks ⁴⁰	1983	42	81	0	19
Ferguson ⁴¹	1984	9	67	22	11
Van Vroonhoven <i>et al.</i> ⁴²	1984	16	63	13	25
Henry and Simson ⁴³	1983	204	58	12	30
Womack <i>et al.</i> ²¹	1988	16	87	0	13
Scheuer <i>et al.</i> ⁴⁴	1989	39	43	26	31
Orrom <i>et al.</i> ⁴⁵	1991	17	59	17	24
Mavrantonis <i>et al.</i> ⁴⁶	1998	20	35		65†

* Includes patients with sphincter reconstruction; † fair/poor combined

and so remains an option for those who have failed or are not candidates for other conservative measures and who wish to avoid a stoma. None the less, it is rarely used by most surgeons because of its poor long-term success rate.

Apposition of sphincter without overlapping

Simple approximation of the internal and external sphincters has been used for primary repair at the time of injury⁵⁰. Such repair has been used for third- and fourth-degree sphincter injuries secondary to obstetric trauma⁵¹ and, in the acute setting, the direct apposition of the sphincters without tension has been reported to give satisfactory results⁵¹. However, Nielson *et al.*³⁴ found that 13 of 24 patients with primary suture of an obstetric tear had a residual endosonographic tear; seven of these 13 patients had no postoperative faecal incontinence. Nevertheless, seven women did have residual faecal incontinence after direct sphincter apposition at the time of obstetric injury. Direct sphincter repair by apposition has been criticized for disappointing results attributed to tearing of sutures and splicing of muscle ends⁵². Arnaud *et al.*⁵³ treated 40 patients with delayed sphincter apposition after obstetric or iatrogenic injury. Complete faecal continence was restored in 25, occasional leak of liquid stool occurred in six, of solid stool in four, and no improvement was evident in 12. Blaisdell⁵⁴ reviewed the technique of direct sphincter apposition and noted a 42 per cent failure rate.

Reefing procedures

In 1882 Warren⁵⁵ described a perineal reefing approach for treatment of anal sphincter injuries, and in the twentieth century anterior reefing emerged as an alternative for reconstruction of thin or damaged sphincters⁵⁶. Stricker *et al.*⁵⁷ recommended this procedure for patients with intact pudendal nerve conduction and a thin perineal body after obstetric injury. Anterior puborectalis reefing in combination with an S-shaped plication of the attenuated anterior external sphincter has also been recommended for patients without pudendal neuropathy or full-thickness external sphincter defects⁵¹. Low preoperative squeeze and resting sphincter pressures diminish the effectiveness of simple reefing procedures that only repair the superficial external sphincter. Extensive reefing procedures that also reconstruct levators and puborectalis may improve continence in 94 per cent of patients. However, despite good initial results with the extensive reefing procedure, loss of control to liquid stool and gas increases with increasing length of follow-up^{57,58}.

Overlapping sphincteroplasty

Direct apposition after obstetric sphincter laceration is usually performed at the time of injury and satisfactory results may be achieved in a tension-free repair in 47–100 per cent of cases (*Table 3*). However haematoma formation,

Table 3 Functional results of overlapping sphincter repair

Reference	Year	No. of patients	Obstetric/operative (%)	Results (%)		
				Excellent	Fair	Poor
Browning and Parks ⁴⁰	1983	97	73	78	13	9
Fang <i>et al.</i> ⁵⁹	1984	79	88	89	7	1
Pezim <i>et al.</i> ⁶⁰	1987	40	100	85	—	—
Stern <i>et al.</i> ⁶¹	1987	11	91	73	17	9
Christiansen and Pedersen ⁶²	1987	12	100	75	5	8
Clerckeko <i>et al.</i> ⁶³	1988	58	69	64	32	26
Laurberg <i>et al.</i> ⁶⁴	1988	19	100	47	—	21
Yoshioka and Keighley ⁶⁵	1989	27	70	74	—	—
Abcarian <i>et al.</i> ⁶⁶	1989	53	40	100	—	—
Fleshman <i>et al.</i> ⁶⁷	1991	55	100	72	22	6
Wexner <i>et al.</i> ⁶⁸	1991	16	100	76	19	5
Fleshman <i>et al.</i> ⁶⁹	1991	28	100	75	21	4
Engel <i>et al.</i> ⁷⁰	1994	55	100	76	24	—
Engel <i>et al.</i> ⁷¹	1994	28	53	75	25	—
Simman <i>et al.</i> ⁷²	1994	14	79	93	7	—
Londono-Schimmer <i>et al.</i> ⁷³	1994	128	64	50	50	—
Oliveira <i>et al.</i> ⁷⁴	1996	55	84	71	29	—
Felt-Bersma <i>et al.</i> ⁷⁵	1996	18	39	72	28	—
Nikiteas <i>et al.</i> ⁷⁶	1996	42	26	67	33	—
Sitzler and Thomson ⁷⁷	1996	31	64	74	26	—
Ternent <i>et al.</i> ⁷⁸	1997	16	100	62	38	—
Gilliland <i>et al.</i> ⁷⁹	1998	77	69	56	44	—

wound infection, faulty technique or an unrecognized second sphincter injury may lead to poor outcome, requiring a second repair in 0.3–5 per cent or more of these patients^{14,80,81}. In those with severe traumatic lesions with significant perineal contamination and associated pelvic injuries, it may be advisable to delay the definitive sphincter repair. Such patients are often best managed by debridement and a diverting colostomy. Secondary repair is only performed after all contaminated perineal wounds have healed and the inflammation has completely subsided.

Overlapping sphincteroplasty is the operation of choice in incontinent patients with isolated anterior defects in the external anal sphincter muscle, particularly in postobstetric trauma. Mobilization, scar excision and direct apposition yields an incidence of sphincter repair disruption of 40 per cent⁵⁴. To avoid this problem, Parks and McPartlin⁸² altered the technique to overlap the muscle ends after scar excision. In 1977, Slade *et al.*⁸³ further modified this technique such that a significant improvement in the functional outcome was achieved compared with initial reports. Specifically, these authors overlapped the sphincters without excision of scar tissue; in addition, the operation was undertaken without faecal diversion. Sitzler and Thomson⁷⁷ assessed the outcome of 31 patients who underwent sphincter repair; in 20 of these patients repair was necessary after obstetric trauma. There was no correlation between the presence or absence of a colostomy and the rate of success or failure. The only difference between these two groups was a significant increase in the mean hospital stay from 14 (range 10–20) to 26 (range 13–60) days owing to the necessity of colostomy closure. Faecal diversion may be useful in cases where there is a history of perianal sepsis, severe perianal trauma or Crohn's disease⁶⁷. Instead of a colostomy, some surgeons have employed bowel confinement to avoid faecal contamination (a 'medical colostomy'). However, a recent prospective randomized surgeon-blinded trial failed to find any advantage conferred by bowel confinement⁸⁴. In this trial 54 consecutive patients who underwent anorectal reconstructive surgery received either a clear liquid diet with antimotility agents until the third postoperative day, or a regular diet commencing from the day of surgery. The first postoperative bowel movement occurred at 3.9 and 2.8 days respectively in the bowel confinement and regular diet groups. There were no significant differences in terms of either morbidity or success. Since bowel confinement does not influence outcome following anorectal reconstructive surgery, it cannot be routinely recommended and is no longer practised by the authors.

Table 3 summarizes the results of overlapping repair for isolated anterior external anal sphincter defects. It is very difficult to interpret the results described in the literature

for a variety of reasons. First, the series are often heterogeneous with respect to sex, age and mechanism of injury. Furthermore, many are small, with relatively short follow-up. Finally, very few of the studies include physiological details. It is only within the last few years that physiological tests have become widely available such that investigators have been able to include both preoperative and postoperative objective data as well as subjective functional evaluation. On the theme of functional assessment, owing to the plethora of staging systems and other means of describing incontinence, it is even more difficult to interpret results. Some surgeons rely on the patient's impression. Others use an incontinence score and some investigators have inadequate definitions such as 'satisfactory' or 'good'. Yet another problem is that many series include patients contributed by groups of surgeons, thereby introducing yet another variable of technique that further obfuscates the data. Lastly, some surgeons employ proximal diversion or bowel confinement while others do not.

One series included a single surgeon's consecutive clinical experience with 77 women, none of whom had a stoma and all of whom had an isolated anterior post-traumatic external anal sphincter defect⁷⁹. The technique of repair included levator plication, overlapping of the ends of the scarred external anal sphincter without any excision of the scar and separate imbrication of the internal anal sphincter muscle. A successful outcome was related to improvement in sphincter function, even in patients over the age of 60 years. There was no correlation between outcome and parity, previous sphincteroplasty, aetiology or duration of faecal incontinence, extent of electromyographic damage, size of endoanal ultrasonographic defect or any manometric variable. Oliveira *et al.*⁷⁴ published a series of 55 women who had sphincteroplasty following faecal incontinence related to anterior sphincter defects. They were followed up prospectively for a mean of 29 months. Fifty-two (95 per cent) had had a vaginal delivery and 30 (55 per cent) had a history of previous anal sphincter repair. In patients over 60 years of age, a significant change in mean squeeze pressure ($P=0.03$) and high-pressure zone length ($P=0.01$) was noted and this correlated with functional outcome (change in incontinence score from 14.3 to 6.4; $P<0.0001$). The authors concluded that a successful outcome after anterior sphincteroplasty is related to improvement of sphincter function, even in an older population. Because age itself was not a predictor of outcome, they felt that patients should not be denied a repair based exclusively on age. This was verified by Simmang *et al.*⁷² in a series of 14 patients of mean age 66 years. However, the relationship between age and outcome is not universally agreed. Sitzler and Thomson⁷⁷ assessed 31 patients who had undergone sphincter repair, 20 after obstetric or traumatic injury.

Whereas the mean age of those who had a successful repair was 39.5 years, that of those in whom the procedure failed was 48.9 years; the difference was deemed significant by the authors. Similarly, Osterberg *et al.*⁸⁵ noted that 'young age' was associated with a favourable outcome, similar to the outcome described by Nikiteas *et al.*⁷⁶. In this latter study, 42 repairs were undertaken by two surgeons over a 5-year period; 32 patients were women and ten were men. Twenty-six of the 32 women had postobstetric injury whereas six presented with iatrogenic defects after fistula repair. One of the predictors of failure was age greater than 50 years. Rasmussen *et al.*⁸⁶ found an even more profoundly adverse effect of age; while a 'satisfactory' continence was achieved in 83 per cent of patients aged under 40 years, only 43 per cent of those aged over 40 years had a 'satisfactory' outcome. Clearly, the issue of the impact of age upon the result of sphincter repair has not been settled. It is certainly disturbing to think that patients aged over 40 years are destined to have a suboptimal sphincter repair.

Pudendal neuropathy as a factor predictive of success following sphincteroplasty has been proposed by a number of authors^{38,69,87} (Table 4). Laurberg *et al.*⁶⁴ analysed a group of 19 patients and reported an 80 per cent success rate in those without neuropathy, compared with only 11 per cent in those with neuropathy ($P < 0.05$). Since that time, Wexner *et al.*⁶⁸, Oliveira *et al.*⁷⁴, Gilliland *et al.*⁷⁹ and others have confirmed this finding. Londono-Schimmer *et al.*⁷³ analysed a group of 94 patients and found that the success rate in individuals without pudendal neuropathy was 55 per cent compared with only 30 per cent in the group with neuropathy ($P < 0.001$). Simmang *et al.*⁷² analysed 10 patients who underwent sphincter repair and reported a 70 per cent success rate in patients without neuropathy and a 20 per cent rate of success in patients with neuropathy. Similarly, Sangwan *et al.*⁸⁸ assessed a group of 15 patients who underwent sphincter repair. All eight patients in whom

both pudendal nerves were normal had a 'good' or 'excellent' functional outcome whereas only one out of six patients with a unilateral pudendal neuropathy had such an outcome. They concluded that both pudendal nerves must be intact to achieve normal continence after sphincteroplasty. Ternent *et al.*⁷⁸ noted that 'a trend towards less improvement in faecal incontinence was noted with bilateral pudendal neuropathy' when describing their 62 per cent success rate in 16 women who underwent sphincter repair. However, as with age, the relationship between pudendal nerve status and the success of repair is not universally accepted. Nikiteas *et al.*⁷⁶ did not identify pudendal neuropathy as a risk factor for failure. Similarly, Rasmussen *et al.*⁸⁶ could not find any relationship between pudendal nerve status and success. Chen *et al.*⁸⁹ and Young *et al.*⁸⁷ were also unable to identify any relationship between pudendal neuropathy and suboptimal outcome.

Intact pudendal nerves are important not only as a possible prognostic factor but also in terms of type and degree of incontinence. Kafka *et al.*⁹⁰ compared 38 consecutive women with primary complaints of either seepage or incontinence of solid stool with 16 asymptomatic women. Both groups of incontinent patients had lower resting and squeeze pressures, more asymmetric high-pressure zones and more rectal hypersensitivity. However, only two factors discriminated between the groups of patients with incontinence to solid stools compared with leakage. First, the rectoanal inhibitory reflex was abnormal in 18 patients with incontinence of solid stools compared with only two of those with leakage ($P < 0.05$). Even more significant was that, while five patients with leakage alone had normal pudendal terminal motor latencies, only seven of those with incontinence of solid stool had bilaterally normal nerves ($P = 0.01$). Furthermore 12 asymptomatic women had bilaterally normal latencies. These findings

Table 4 Effect of pudendal neuropathy on the outcome of anterior sphincter repair:

Reference	Year	No. of patients	Success rate (%)		P
			No neuropathy	Neuropathy	
Laurberg <i>et al.</i> ⁶⁴	1988	19	80	11	<0.05
Wexner <i>et al.</i> ⁶⁸	1991	16	92	50	n.s.
Engel <i>et al.</i> ⁷⁰	1994	55	—	—	n.s.
Simmang <i>et al.</i> ⁷²	1994	10	70	20	n.s.
Londono-Schimmer <i>et al.</i> ⁷³	1994	94	55	30	<0.001
Sitzler and Thomson ⁷⁷	1996	31	67	63	n.s.
Felt and Bersma ⁷⁵	1996	18	—	—	n.s.
Sangwan <i>et al.</i> ⁸⁸	1996	15	100	14	<0.005
Gilliland <i>et al.</i> ⁷⁹	1998	77	63	10	<0.01

n.s., Not significant

have been further confirmed by two other series^{74,79}. Table 5 summarizes the factors predictive of success^{76,79}.

A recent prospective trial has highlighted the importance of scar preservation during sphincteroplasty⁹³. Twelve consecutive women with isolated anterior external anal sphincter defects all underwent preoperative anal manometry, electromyography, assessment of pudendal nerve terminal motor latency and endoanal ultrasonography. Intraoperative ultrasonography was performed in the operating room after repair. Three types of repair were identified: muscle to muscle, muscle to scar, and scar over scar. These types corresponded to hyperechoic–hyperechoic, hyperechoic–hypoechoic and hypoechoic–hypoechoic. At a mean follow-up of 5 (range 2–12) months the preoperative and postoperative incontinence score in the five patients with a hyperechoic–hyperechoic or hyperechoic–hypoechoic scar was 17.8 (range 15–22). At follow-up the mean score had decreased to only 10.9 (range 4–15). Conversely, seven patients in whom a hypoechoic–hypoechoic repair was achieved had a mean preoperative incontinence score of 16.7 (range 7–20) which had decreased to 2.1 (range 0–8) at the time of follow-up.

Rosenberg and Kehlet⁹⁴ studied 20 consecutive patients who underwent overlapping external anal sphincter repair between March 1993 and May 1997. These patients were in an accelerated stay programme that included preoperative information, no premedication, no stoma, single-dose prophylactic antibiotic, paracetamol for analgesia, free oral fluid and food immediately after the operation, laxatives and enforced mobilization; the median hospital stay was 1 day. Fifteen patients were discharged on the day after surgery and the other five patients at 48 h after operation. There was

no 30-day morbidity, no patient received a colostomy, and 14 of the 19 patients available for follow-up at a mean of 14 months reported a significantly improved functional result compared with their preoperative state. The authors concluded that the accelerated stay programme for overlapping repair of the external anal sphincter is safe.

In summary, the optimal conditions before repair are no previous repair, preservation of scar, bilaterally intact pudendal nerves, normal rectal sensation and an asthenic young patient with an isolated anterior external anal sphincter defect (Table 6).

Total pelvic floor repair

Total pelvic floor repair (TPR) refers to a combination of anterior external sphincter plication with levatorplasty and postanal repair. The indications include complicated injuries to the external sphincter and puborectalis at one or more sites, and pudendal neuropathy⁹⁵. TPR may be

Table 6 Optimal conditions for sphincter repair

Preoperative	
No previous repair	
Scar present	
Bilateral intact pudendal nerves	
Normal rectal sensation	
Asthenic patient	
Young patient	
Intraoperative	
Overlapping scar	
Increased resting and squeeze pressure	
Increased high-pressure zone	

Table 5 Predictive factors of success of anal sphincter repair

Reference	Year	No. of patients	Positive	Not significant
Chen and Luchtefeld ⁶⁹	1998	12		PNTML
Briel <i>et al.</i> ⁹¹	1998	24 old 31 new		RV septum repair, IS imbrication, ES repair
Young <i>et al.</i> ⁸⁷	1998	56		Age, neuropathy
Ternent <i>et al.</i> ⁷⁸	1997	16	Restoration of anal canal pressure	PNTML
Sitzler and Thomson ⁷⁷	1996	31	Persistent anal sphincter defect	Stoma Manometry
Nikiteas <i>et al.</i> ⁷⁶	1996	42	Obese, older than 50 years, perineal descent	
Khanduja <i>et al.</i> ⁹²	1994	48	Not stated	Anorectal angle
Orrom <i>et al.</i> ⁴⁵	1991	16		Previous repair of RV fistula, perineal wound infection
Fleshman <i>et al.</i> ⁶⁷	1991	55		
Fleshman <i>et al.</i> ⁶⁹	1991	28	Squeeze pressure	
Ctercteko <i>et al.</i> ⁶³	1988	58	Age, duration of incontinence	
Parks and McPartlin ⁸²	1971	20	Temporary colostomy	

PNTML, pudendal nerve terminal motor latency; IS, internal sphincter; ES, external sphincter

undertaken in one (primary) or two (secondary) stages, with or without a colostomy, and has been shown to decrease pelvic floor descent without influencing resting and squeeze anal canal pressures⁹⁶. TPR in 22 women with neurogenic faecal incontinence resulted in return of full continence of solids, liquids and flatus after primary and secondary repairs in nine and two patients, respectively; however, as with postanal repair, clinical improvement did not correlate with anorectal angle change. Deen *et al.*⁹⁷ undertook a randomized trial to compare three methods of repair for neuropathic faecal incontinence. They compared postanal repair, levatorplasty and TPR in 36 women (12 in each group) and concluded that TPR is a viable option for idiopathic incontinence. However, physiological investigations were not performed, and factors like pudendal nerve terminal motor latency may have affected the results. Two years later the same authors performed a prospectively randomized trial comparing TPR (with or without extensive submucosal and intersphincteric dissection) and TPR plus internal sphincter plication in 33 women (18 TPR alone and 15 TPR with plication)⁹⁸. The results demonstrated that the plication did not influence the overall improvement in anorectal function obtained by TPR. In addition, it was associated with a significant reduction in both anal resting and squeeze pressures. End-to-end plication of the internal anal sphincter was associated with an improvement in high-pressure zone in these authors' initial series of sphincteroplasty patients⁹⁶.

Neosphincter procedures

Bilateral gluteus maximus transposition (gluteoplasty)

Gluteoplasty was first described in 1902⁹⁹. Since then at least 81 patients have been reported in the literature to have undergone this operation, 49 (60 per cent) of whom were noted to have had a 'good' outcome. As for many operations, a variety of results have been published (Table 7). Pearl *et al.*¹⁰⁹ reported five men and two women who underwent this operation for a variety of indications. While six of the seven patients were continent of stool, only two were continent of liquid and only one of flatus after surgery. At the other end of the spectrum are the results reported by Christiansen *et al.*¹¹⁰; none of seven patients who underwent bilateral gluteus maximus transposition achieved continence of liquid and only three were continent of solid stool, leading the author to conclude that the rate of 'satisfactory' results was zero. Between these two extremes lies the result of Devesa *et al.*¹¹². They reported 20 patients (12 women and eight men) who ranged in age from 15 to 58 years. 'Normal control' was achieved by nine patients,

Table 7 Results of unstimulated bilateral gluteoplasty

Reference	Year	No. of patients	Results (no. of patients)	
			Good	Fair
Chetwood ⁹⁹	1902	1	1	—
Schoemaker ¹⁰⁰	1909	6	6	—
Bistrom ¹⁰¹	1944	3	2	1
Bruining <i>et al.</i> ¹⁰²	1981	1	2	—
Prochiantz and Gross ¹⁰³	1982	15	9	1
Hentz ¹⁰⁴	1982	5	4	—
Skef <i>et al.</i> ¹⁰⁵	1983	1	1	—
Iwai <i>et al.</i> ¹⁰⁶	1985	1	1	—
Chen and Zhang ¹⁰⁷	1987	6	3	1
Onishi <i>et al.</i> ¹⁰⁸	1989	1	1	—
Pearl <i>et al.</i> ¹⁰⁹	1991	7	4	2
Christiansen <i>et al.</i> ¹¹⁰	1985	7	0	3
Devesa <i>et al.</i> ¹¹¹	1992	10	6	3
Devesa <i>et al.</i> ¹¹²	1997	20	9	1

including 'excellent' or 'good' results in six and three respectively, with a 'bad' result in seven. Yoshioka *et al.*¹¹³ reported the results of a prospective randomization of 24 patients to either TPR or gluteus transposition for postobstetric neuropathic faecal incontinence. No differences were noted between the two groups relative to either subjective outcome or changes in preoperative and postoperative scores at a mean of 10 (range 6–27) months of follow-up. A 'good' result was achieved in seven patients (58 per cent) in each group. In the TPR group, the preoperative incontinence score decreased from 13.1 to 6.6 after operation while a change from 13.8 to 7.7 was noted in the gluteoplasty group. Failures were attributed to suture disruption, poor muscular contraction and intractable constipation.

Graciloplasty

Gracilis transposition was undertaken initially in an attempt to treat children with faecal incontinence due to neurological and congenital abnormalities¹¹⁴. The tendon of the gracilis muscle was transposed around the anus and anchored to the contralateral ischial tuberosity. The basic concept was to create a natural barrier to the passage of stool. However, since the gracilis is a skeletal muscle it can be fatigued easily. In 1981 Salmons and Henriksson¹¹⁵ introduced a technique whereby fatiguable muscles could be transformed into non-fatiguable muscles, leading to the concept of stimulated gracilis muscle (Table 8). The stimulated graciloplasty operation has been used for the treatment of incontinence secondary to trauma and neurological causes, and in patients with anorectal agenesis.

Table 8 Results of gracilis transposition

Reference	Year	No. of patients	Successful outcome (%)	Infection (%)
Pickrell <i>et al.</i> ^{114*}	1952	34	100	—
Salmons and Henriksson ^{115*}	1981	—	—	—
Williams <i>et al.</i> ¹¹⁶	1991	6	0	—
Baeten <i>et al.</i> ¹¹⁷	1988	1	—	—
Cavina <i>et al.</i> ¹¹⁸	1987	32	62	3
Konsten <i>et al.</i> ¹¹⁹	1993	26	65	8
Seccia <i>et al.</i> ¹²⁰	1994	75	71	—
Baeten <i>et al.</i> ¹²¹	1995	52	73	—
Kumar <i>et al.</i> ¹²²	1995	10	90	—
Wexner <i>et al.</i> ¹²³	1996	17	60	—
Altomare <i>et al.</i> ¹²⁴	1997	9	44	—
Lubowski <i>et al.</i> ¹²⁵	1996	—	—	—
Geerdes <i>et al.</i> ¹²⁶	1996	67	78	12
Mander <i>et al.</i> ¹²⁷	1999	64	56	—

*Non-stimulated status; all other series were stimulated

The muscle may be stimulated either via the nerve trunk or via the intramuscular portion of the main nerve. The difference between the stimulated operation and the original graciloplasty is not only the electrostimulation, but the fact that muscle rather than tendon is transposed to ensure a dynamic neosphincter. Dynamic graciloplasty is indicated in patients with severe faecal incontinence for whom standard therapy has failed or is not expected to be efficacious. Patients must have a rectum, anal canal and anatomically present (although obviously injured) sphincter. Contraindications to a current US trial include age under 18 or over 80 years, non-functioning gracilis muscle, cancer of anorectum or colon, anal agenesis, chronic intractable diarrhoea, inflammatory bowel disease and pregnancy.

Baeten *et al.*¹²¹ have reported the largest single-centre series of stimulated graciloplasties. Fifty-two patients had surgery, including 12 with anal atresia, and were analysed at a mean follow-up of 2.1 years; 38 of the 52 were continent. These patients also noted significant improvement in quality of life as assessed by the Nottingham Health Profile¹²⁸ and the State Trait Anxiety Inventory¹¹⁰. The mean evacuation frequency had been five per 24 h before transposition and this decreased significantly to two per 24 h at 8 weeks after surgery. Perhaps of even greater significance was that the median time to defer the call to stool increased from only 9 s before stimulation to 19 min at 52 weeks. Similarly, the mean enema retention time increased from 0 s to 3 min at 52 weeks of follow-up. Early in the series sepsis was a problem and resulted in explantation in two of the first 15 patients, but in the next 37 patients only two stimulation devices required removal.

Subsequently, Geerdes *et al.*¹²⁶ from the same centre reported a series of 67 patients who underwent dynamic graciloplasty. The success rate has reached 78 per cent. Failure was attributed to rectal sensory or distension problems, poor neosphincter contraction, sepsis and perforation. Eighteen per cent of patients with moderate postoperative constipation were treated successfully by biofeedback and laxatives. This study also reported a high incidence of complications, but most were preventable or treatable. A number of patients required exchange of leads owing to infection, tendon shortening for loose wrap, stimulator replacement and repositioning for displacement. Altomare *et al.*¹²⁴ had similar problems with sepsis and technical complications. Lubowski *et al.*¹²⁵ described 12 patients in whom stimulated graciloplasty was undertaken, five of whom had undergone an abdominoperineal resection; infection was a prominent early complication. In most series graciloplasty is associated with a high morbidity rate but technical improvements as well as better patient selection can reduce this. Because of this high morbidity rate, patients must be psychologically and emotionally prepared for an eventual stoma. To select the most appropriate candidates, knowledge of predictive factors of success would be helpful.

Korsgen and Keighley¹²⁹ suggested that poor rectal sensation augured procedural failure. Patients with poor sensation may have incomplete evacuation requiring routine periodic enema washouts. Indeed the most important variables relating to successful outcome after stimulated graciloplasty are appropriate rectal sensitivity and compliance. Both Baeten *et al.*¹²¹ and Korsgen and Keighley¹²⁹ have noted that the operation is less apt to be successful in patients with impaired rectal sensation.

More recently, Mavrantonis *et al.*¹³⁰ compared 17 patients who underwent direct nerve stimulation with 16 patients who underwent intramuscular electrode placement. Although there were no differences between the two groups relative to non-device-related morbidity, there was a significant difference ($P=0.006$) favouring intramuscular lead placement. Thus the technical variable most predictive of success is the type of stimulating device used. The avoidance of fibrosis and increasing levels of impedance favours the intramuscular lead apparatus and stimulating device. Age at surgery does not correlate with degree of postoperative improvement of continence score nor does the duration of symptoms or body habitus. Similarly, the aetiology of the incontinence does not influence the outcome nor does the severity of preoperative incontinence, as assessed by the incontinence score. A history of previous surgery for anal incontinence, early postoperative morbidity and any of the data obtained from physiological investigation (manometric pressures, endoanal ultrasono-

graphy, electromyography and pudendal nerve terminal motor latency findings) do not predict outcome. Furthermore, the differences between the preoperative resting and squeeze pressures and the stimulated resting and squeeze pressures 6 months after surgery do not contribute to the ultimate prognosis. Thus anal pressures may not be an adequate indicator of the success of the procedure. Although anal manometry may be relatively insensitive as a predictor of outcome, at present it appears to be the best test for quantifying muscle function. Clearly, a more accurate tool needs to be developed that should allow an assessment which correlates with clinical outcome.

Results have been published of a modification of stimulated graciloplasty¹³¹, in which sphincter resolution was performed using one gracilis muscle wrapped around the anus by the split-sling technique. Twenty-seven patients underwent this procedure with 18 achieving continence of solid and liquid stool. The preliminary results of a prospective multicentre trial using the electrically stimulated gracilis neosphincter demonstrated a significant improvement in incontinence scores following stoma closure in 44 of 51 patients studied¹²⁷.

Bilateral non-stimulated graciloplasty

Kumar *et al.*¹²² reported ten patients of mean age 39 (range 8–73) years with a variety of conditions who underwent a bilateral non-stimulated graciloplasty. At a mean follow-up of 24 (range 6–40) months, nine were 'fully continent'. Objective physiological correlation with the subjective claim included a significant increase in resting pressure from 16 to 78 cmH₂O ($P < 0.01$) and similar increases in squeeze pressures (44 to 121 cmH₂O; $P < 0.01$) and high-pressure zone length (1 to 2 cm; $P < 0.01$). The bilateral non-stimulated graciloplasty may be a viable option in health care systems in which neither the technical expertise nor financial resources for stimulated graciloplasty are available.

Artificial bowel sphincter

Successful use of an anal artificial bowel sphincter was first reported by Christiansen and Lorentzen¹³² in 1987. Christiansen and Sparso¹³³ subsequently documented their initial experience of five patients with neurogenic incontinence. A modified artificial sphincter was created in 1992 and implanted in 12 patients with an 80 per cent success rate at a 6-month follow-up. However, by 19-month follow-up two devices had become infected requiring explantation and eight revisions had been undertaken in four patients. Overall, ten neosphincters remained functioning for more than 6 months (Table 9).

Table 9 Results of artificial bowel sphincter

Reference	Year	No. of patients	Successful outcome (%)
Christiansen and Lorentzen ¹³²	1987	2	—
Christiansen and Sparso ¹³³	1992	12	83
Wong <i>et al.</i> ¹³⁴	1996	12	75
Lehur <i>et al.</i> ¹³⁵	1999	24	70
O'Brien and Skinner ¹³⁶	1999	9	88

Wong *et al.*¹³⁴ reported 12 patients who underwent implantation of an artificial anal sphincter, all of whom had failed 'conservative treatment'. At a mean follow-up of 58 months a 33 per cent morbidity and a 75 per cent success rate (nine of 12 patients) were noted. The average activated pressure was 68 mmHg whereas the preoperative pressure had been only 16 mmHg; none of the patients noted postoperative evacuatory difficulties. Salvage was possible in patients whose complications were infection, leaking balloon, a leaking pump, a leaking cuff and pain. One patient in whom infection occurred required explantation of the device. Similarly, Lehur *et al.*¹³⁵ reported their results in 24 consecutive patients (seven men) of mean age 46 (range 14–80) years implanted for more than 6 months at three centres. At a median follow-up of 16 (range 6–31) months, seven patients had had their devices explanted; reimplantation was performed successfully in four patients. At the end of follow-up, 21 patients had an activated device in place. The mean faecal incontinence score dropped from 100 before operation to 24, 36 and 31 at 6 months, 1 year and at the end of follow-up respectively. Mild (seven) and severe (two) evacuation disorders occurred. A high degree of satisfaction was achieved in 16 patients in the total series and two reimplanted patients were waiting for activation. Mean anal pressures increased from 32 (range 5–76) mmHg before operation to 60 (range 38–96) mmHg at the end of follow-up.

O'Brien and Skinner¹³⁶ described the use of an artificial bowel sphincter in nine patients. The mean operative time was 65 min and the median length of hospital stay was 3.6 days, with no postoperative complications. However, in two patients the artificial bowel sphincter was removed, one at 7 months because of infection and the other at 3 months because of extrusion of the device. The artificial bowel sphincter was activated in eight patients, all of whom became fully continent of both solid and liquid stool. The mean incontinence score fell from 17.3 before operation to 1.8 at postoperative follow-up and the measure of quality of life (SF36) also indicated marked improvement. The artificial bowel sphincter, still at an experimental stage,

appears to be a valid alternative to a permanent colostomy in patients with anal incontinence due to neurological disorders and in those for whom other procedures for faecal incontinence (such as sphincter repair) have failed. The predictive variable of success, although hard to control, is avoidance of infection.

Sacral nerve stimulation

An option for treatment of patients with weak but intact anal sphincters is sacral nerve stimulation. Stimulation of sacral nerves for the treatment of urinary difficulties was first described in 1960¹³⁷ but Matzel *et al.*¹³⁸ were the first to report its use in faecal incontinence in 1995. Patients initially undergo a short trial of stimulation using percutaneous electrodes (usually placed through S3 foramen) and an external stimulator. If there is symptomatic improvement over several days the patient proceeds to implantation of a permanent electrode and a stimulator. The permanent electrode is placed through an incision over the sacrum; the leads are tunnelled to the stimulator, which is implanted in the anterior abdominal wall. Matzel *et al.* described a marked improvement in faecal incontinence and external sphincter pressures in three patients who received a permanent implant. Subsequently Vaizey *et al.*¹³⁹ reported short-term effects of sacral nerve stimulation in 12 patients, and demonstrated that sacral nerve stimulation seemed to facilitate external anal sphincter muscle activity, resulting in an increase in squeeze pressure, decrease in rectal contractility, and a possible stabilization of the anal resting pressure. Vaizey *et al.*¹⁴⁰ subsequently published the first double-blind crossover study of sacral nerve stimulation for faecal incontinence. They reported two patients with passive faecal incontinence who had been implanted for 9 months with a permanent sacral nerve stimulator and electrode. The trial period consisted of two 2-week periods, with the stimulator turned on for 2 weeks and off for 2 weeks. They concluded that there was a marked, unequivocal improvement in faecal incontinence; quality-of-life measurements also showed a marked improvement at 9 months after permanent stimulation. At present, data on this technique are scant. Larger prospective studies with longer follow-up are needed to validate these initial results.

Procon device

Another new method, although not surgical, is the Procon device (Anatec LLC, Houston, Texas, USA)¹⁴¹ (Fig. 1). This mechanism is essentially a 6.7-mm diameter soft plastic catheter, one end of which is an inflatable balloon to prevent faecal accidents. The balloon is inflated by the

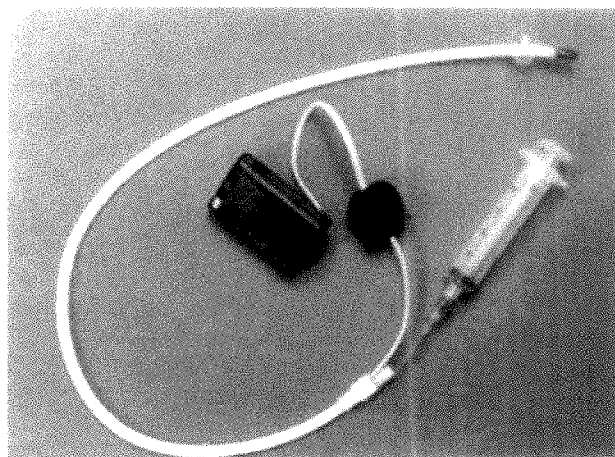


Fig. 1 Procon device

patient after transanal introduction of the lubricated catheter. On the end of the balloon is a microprocessor sensor which is attached by wire to a device worn on the patient's waist. The device alerts the patient to the presence of stool in the rectum so that he or she may go to a convenient location, deflate the balloon and remove the catheter. After evacuating the rectum the catheter can be reinserted. Although the device is still at an experimental stage, it shows promise in preliminary use.

Conclusion

The literature is replete with hypotheses and theories about reasons for the success or failure of various operations designed to correct faecal incontinence. The number of operations and the methods by which they are performed seem limited only by the surgeon's imagination. A common feature of all the publications to date is that they are, to a degree, heterogeneous and subjective. Given the limitations of the available literature one can only make conclusions based on a consensus opinion. As with most operations, case selection is of utmost importance; unfortunately the literature does not help clarify which patients to select for the various operations. None the less, based upon the predictive variables outlined in this review, Fig. 2 is offered as an algorithm for the surgical management of patients with faecal incontinence.

Acknowledgements

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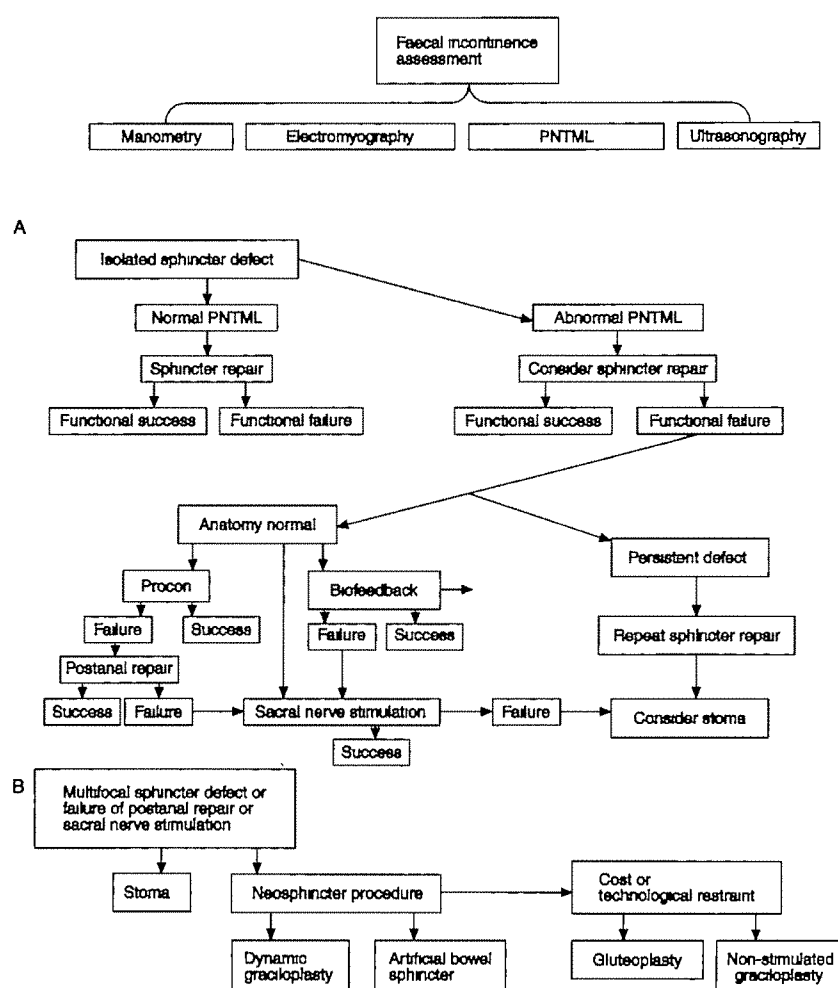


Fig. 2 Algorithm for the management of faecal incontinence. PNTML, pudendal nerve terminal motor latency

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Professor Seiki Matsuno, Chief Editor of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the April to June 2000 issues of the journal for this quarter's digest. A digest of *BJS* for the same period written by Professor Pierre Guille, Associate Editor, appears in the Japanese journal.

Oesophagus

Some authors attempted to clarify the problems of pulmonary thromboembolism (PTE), which occurs less frequently in Japan than in the West, in respect of its special perioperative management and prophylaxis after oesophagectomy¹. They studied 26 patients with PTE following oesophagectomy among 1023 patients with oesophageal cancer between 1984 and 1997. The presence of embolism was confirmed by pulmonary perfusion scintigraphy. Incidence, diagnosis and other issues of PTE were reviewed. The incidence of PTE was 2.5 per cent, with patients having a biphasic early and late onset. The main symptoms were dyspnoea in 19 patients and tachycardia in 17. Scintigraphy demonstrated 154 lesions, 35.7 per cent of which were located in the left lower lobe and 25.3 per cent in the right lower lobe. Treatment consisted mainly of the administration of heparin and urokinase. Four of the 26 patients died. Intermittent pneumatic compression with the administration of heparin was used from 1994 to prevent PTE, and this also helped to decrease the incidence from 3.2 to 0.7 per cent. Because the incidence of PTE following oesophagectomy is higher than expected, PTE should be considered whenever hypoxaemia of some unknown cause is found. Both early diagnosis and treatment are essential. It is also important to prevent PTE by the use of pneumatic compression.

Stomach

Brain metastasis from cancer of the gastrointestinal tract is uncommon; brain metastasis from gastric cancer is rare and its incidence is low². Brain metastasis from gastric cancer is often difficult to treat and is resectable in only a few cases. The authors of one study treated three patients who had a solitary brain metastasis after gastrectomy. These three cases are reviewed along with eight other previously reported cases of brain metastasis to clarify the clinicopathological features and to suggest guidelines for patients with metastatic brain tumours. The clinicopathological features of 11 patients with brain metastasis were analysed. For comparison purposes, the 11 cases were classified into three groups as follows: a resection group, a chemoradiotherapy group and a non-treatment group. All the patients had advanced gastric cancer of stage III or more. The resection group had the most survivors, and survival rates decreased in the order of the resection group, the

chemoradiotherapy group and the non-treatment group. There was a statistically significant difference between the resection group and the non-treatment group ($P = 0.0177$). Aggressive multidisciplinary treatment, including resection for brain metastasis, should improve the quality of life and prolong life expectancy.

Colon and rectum

The first step in liver metastasis is venous invasion by cancer cells from the primary tumour³. However, even among patients whose histology shows extensive venous invasion by the primary tumour, cases without synchronous liver metastases are sometimes found. As a result, there is a strong possibility that, besides the established causes of colorectal cancer and that of cancer cells invading the veins, some other important causes for liver metastasis must exist. The authors investigated the expression rates of CD44, proliferating cell nuclear antigen (PCNA) and vascular endothelial growth factor (VEGF) in 28 primary colorectal tumours using immunohistological techniques, and examined an association with liver metastasis. Patients strongly positive for CD44 or PCNA had a higher rate of synchronous liver metastases than those with either no expression or a low level of expression. The authors could not find any correlation between VEGF expression and synchronous liver metastasis. In patients with severe venous invasion, VEGF was not correlated with liver metastases, whereas CD44 and PCNA were correlated with liver metastasis. In patients in whom severe venous invasion is observed histologically, an immunohistochemical analysis for CD44 and PCNA should be done to assess the likelihood of liver metastases.

The effect of intraoperative colonic lavage with *N*-nitro-L-arginine methyl ester (L-NAME) on the healing of colonic anastomosis in the presence of a left-sided obstruction was investigated in the rat⁴. Left-sided colonic obstruction was created in 144 Wistar rats. The obstruction site was excised 24 h later and anastomosis was performed after either no irrigation or colonic lavage with either saline, povidone-iodine (PI), short-chain fatty acids (SCFAs), L-NAME or glutamine (24 animals each). Animals were killed on days 3 and 6, and a 4-cm colonic segment with the anastomosis at the centre was excised. Bursting pressure (BP) and hydroxyproline (HP) content were measured. In the saline, PI and SCFA groups, BP was higher ($P < 0.05$, $P < 0.05$ and $P < 0.001$ respectively) and HP concentration

was similar compared with controls. Both the BP and HP concentrations were higher in the glutamine group than in controls ($P < 0.001$). BP was lower ($P < 0.05$) and HP concentration was similar in the L-NAME group compared with the control group. Colonocyte nutrition and tissue perfusion are the mainstays of anastomotic healing. Intraoperative colonic lavage with L-NAME suppresses colonic anastomotic healing in the presence of a left-sided obstruction.

The technique of laparoscopically assisted colectomy (LAC) was developed for benign and malignant diseases of the colon and rectum; however, its feasibility and the associated clinical outcome remain unclear⁵. Forty-five patients were reviewed who underwent LAC along with 62 patients who underwent traditional open surgery for colorectal carcinoma; clinical data were compared in an effort to determine whether LAC is really minimally invasive and whether it enhances the quality of life. To make the backgrounds of the patients in both groups almost the same, the authors compared data only from patients with colorectal carcinoma of stages 0, I and II. The duration of surgery in the open group was significantly shorter for all procedures except sigmoid resection, but the blood loss was not significantly different between any of the procedures except for right colectomy. The time to the first passing of flatus and restarting oral intake, length of hospital stay and duration of epidural analgesia were significantly shorter in the LAC group. The morbidity and mortality rates in the LAC group were almost the same as those in the open group at 30 and 3 per cent versus 23 and 2 per cent respectively. However, five major complications of LAC for advanced colorectal carcinoma might be prevented by performing an open procedure. In conclusion, LAC is a safe and minimally invasive surgical technique following which one may expect a faster recovery, but patients with advanced colorectal carcinoma must be selected carefully for this operation.

Liver

Intrahepatic lithiasis (IHL) is a very rare disease in Europe and no 'gold standard' treatment has yet been codified⁶. The aim of one study was to report a personal experience of IHL detected in 20 patients (six men and 14 women) between January 1982 and December 1991. Eleven of these patients presented with IHL alone, seven had IHL associated with gallbladder or common bile duct stones, and two were affected by secondary IHL caused by previous biliodigestive anastomosis-induced stricture. The diagnosis was determined by cholangiography in all patients, by ultrasonography in 19 and by computed tomography in 14. The surgical procedures used were as follows: liver resection in 12 patients, various types of biliodigestive anastomosis in

six, and choledocholithotomy with simultaneous removal of stones from the hepatic duct in two patients. The intraoperative mortality rate was nil. Complications consisted of two subphrenic abscesses, one septicaemia and one bowel occlusion. Two patients were lost to follow-up, two died 2 years after surgery for reasons not connected with the disease, one died from suppurative cholangitis 6 months after surgery, and two had recurrent stones and were treated by extracorporeal lithotripsy and endoscopic stone removal; the remaining 13 patients remained symptom free at follow-up which varied between 6 months and 11 years. Liver resection is the treatment of choice when IHL is confined to one lobe of the liver. When IHL affects the entire liver, resection of the main involved area should be performed whenever possible. Other options include hepatoduodenal anastomosis using the interposed jejunal loop to enable endoscopic or combined treatment of recurrent stones.

To clarify the changes that occur in hepatic venous oxygen saturation ($ShvO_2$) during hepatic ischaemia-reperfusion (I/R) injury, the relationship between $ShvO_2$, hepatic tissue blood flow (HTBF) and portal vein pressure (PVP) was examined in a warm I/R model using pig livers⁷. Female pigs weighing 18–23 kg were subjected to warm I/R under extracorporeal circulation between the superior mesenteric vein and the left jugular vein to avoid portal congestion. The warm ischaemic times were 120 min ($n = 4$), 180 min ($n = 14$) and 240 min ($n = 4$). $ShvO_2$, HTBF and PVP were measured after reperfusion. The survival rates of the pigs 3 days after reperfusion were 100 per cent in the 120-min group, 57 per cent in the 180-min group and 25 per cent in the 240-min group. In the 180-min group, the $ShvO_2$ was lower in the pigs that died than in those that survived. There was a significant correlation between $ShvO_2$ and both PVP and HTBF after reperfusion. Histological examination revealed findings of severe I/R injury in pigs with a low $ShvO_2$ and mild I/R injury in animals with a stable $ShvO_2$. These observations suggest that the changes in $ShvO_2$ might reflect the degree of hepatic I/R injury, especially that related to microcirculatory disturbances occurring at the sinusoid levels.

Other authors analysed the changes in serum levels of interleukin (IL) 6, human hepatocyte growth factor (hHGF) and type IV collagen 7S (7S) during the perioperative period of hepatectomy and evaluated their relationship with systemic inflammatory response syndrome (SIRS)⁸. The study subjects comprised 40 patients who underwent hepatectomy. Postoperative SIRS was observed in 14 patients. Between patients with and without SIRS there were significant differences in the preoperative values of prothrombin time, hepaplastin test, cholinesterase and indocyanine green retention at 15 min ($P < 0.01$). Compared with levels in patients without SIRS, the IL-6,

hHGF and 7S levels in those with SIRS fluctuated in a higher range and remained significantly higher after postoperative day 1 ($P < 0.05$). Eight of 14 patients with SIRS had postoperative complications. In the eight patients with SIRS who had postoperative complications and in the four patients in whom the SIRS state lasted 3 days or longer, 7S levels were significantly higher during the perioperative period ($P < 0.05$). In patients with SIRS the postoperative levels of IL-6 and hHGF, as well as preoperative and postoperative levels of 7S, were raised. The authors consider these levels to be risk factors for complications during the perioperative period of a hepatectomy.

Cardiovascular surgery

The purpose of one study was to clarify whether or not severe myxomatous degeneration impairs the stability of a repaired mitral valve after valve-conservative surgery⁹. A total of 21 patients who underwent successful valve-conservative surgery for pure isolated mitral incompetence were classified into two groups, one comprising those with stable mitral valve function and the other comprising those who developed recurrent incompetence within 1 year after surgery. The histological severity of myxomatous degeneration of the mitral leaflet was compared between the two groups, based upon microscopic observation and quantification of the myxomatous area in the fragment that had been surgically excised from the floppy mitral leaflet during valve-conservative surgery. The degree of myxomatous degeneration of the surgically excised fragment was significantly higher in the 'recurrent' group than in the 'stable' group ($P = 0.02$). As a microscopically confirmed, severely degenerative myxomatous mitral valve may develop recurrent incompetence within a relatively short period after valve-conservative surgery, careful and regular follow-up is required.

Although minimally invasive direct coronary artery bypass (MIDCAB) eliminates the need for median sternotomy and cardiopulmonary bypass, its indications are limited¹⁰. Conversely, coronary artery bypass without cardiopulmonary bypass (off-pump bypass) enables complete surgical revascularization under an optimal surgical field established by median sternotomy, even if patients have multivessel disease. This study was designed to determine the invasiveness of median sternotomy by comparing 11 patients who underwent MIDCAB and five who underwent off-pump bypass between May 1997 and April 1998. There were no significant differences between the MIDCAB group and the off-pump group in mean age (57 *versus* 66 years), mean operating time (321 *versus* 441 min), mean number of grafts (1.0 *versus* 1.4 per patient), mean peak creatine kinase (CK) value (662 *versus* 609 units/

l), mean peak CK-muscle-brain values (12 *versus* 16 units/l) and mean postoperative blood loss (369 *versus* 541 ml). Although there was no significant difference in peak C-reactive protein level, the time taken until normalization of c-reactive protein were shorter in the MIDCAB group than in the off-pump group at 7 *versus* 15 days ($P > 0.01$). The mean hospital stay was not different between groups at 16 *versus* 26 days. These findings suggest that off-pump bypass is more invasive than MIDCAB, which may be attributable to the median sternotomy.

Lung

Various preoperative and operative factors were evaluated to identify the predictors of improvement in forced expiratory volume in 1 s (FEV₁) after lung volume reduction surgery (LVRS)¹¹. Fifty-eight patients with emphysema received bilateral LVRS either via a sternotomy ($n = 53$) or by thoracoscopy ($n = 5$). The patients were divided into the following two groups: group I ($n = 17$), patients whose FEV₁ improved by less than 20 per cent; and group II ($n = 41$), patients whose FEV₁ improved by at least 20 per cent. The preoperative factors (age, degree of dyspnoea, oxygen use, steroid use, pulmonary function test, arterial blood gas, pulmonary haemodynamics, 6-min walking distance) and operative factors (removed lung weight, number of staplers) were similar between the two groups. Upper lobe type emphysema was noted more frequently in group II and the average improvement in FEV₁ was significantly better in patients with upper lobe type emphysema (62.8 per cent) than lower lobe type (36.9 per cent) and mixed type (35.5 per cent) ($P < 0.01$). Severe pleural adhesion was more frequently found in group I and the average improvement in FEV₁ was also significantly lower in patients with severe pleural adhesion (19.8 per cent) than mild-to-moderate adhesion (46.8 per cent) and no-to-minimal adhesion (62.3 per cent) ($P < 0.01$). These results suggest that upper lobe type emphysema may be a predictor of better FEV₁ improvement, while severe pleural adhesion is considered to be a predictor of poorer FEV₁ improvement after bilateral LVRS.

The aim of another study was to investigate the changes in atrial natriuretic peptide (ANP) levels and lung guanosine 3',5'-cyclic monophosphate (cGMP) concentrations caused by pneumonectomy, and the effect of inhaled nitric oxide after pneumonectomy in a canine model¹². The mean pulmonary arterial pressure (PAP) and plasma ANP levels were measured over 180 min in two groups of dogs that underwent pneumonectomy, one subjected to 60 min of 5 p.p.m. nitric oxide inhalation ($n = 5$) and one subjected to 180 min without nitric oxide inhalation ($n = 5$). The ANP and cGMP levels in the lung were also measured before and

after pneumonectomy. Both the PAP and ANP levels increased significantly. Inhaled nitric oxide rapidly reduced the PAP and plasma ANP to levels similar to those before pneumonectomy. The lung ANP level was significantly increased after pneumonectomy, but inhaled nitric oxide reduced it to a level similar to that before pneumonectomy. The lung cGMP level, which was significantly decreased after pneumonectomy, was significantly increased by nitric oxide inhalation. These results indicate that nitric oxide administration may be effective in preventing pulmonary hypertension after pneumonectomy, although an increase in ANP concentration does not reduce the PAP.

Various surgical procedures have been developed in an attempt to alleviate the significant problems caused by chronic pleural empyema¹³. One study evaluated an 11-year experience of employing a number of therapeutic approaches. Between 1987 and 1997, 45 consecutive patients underwent treatment for chronic empyema. They comprised 21 patients presenting after tuberculosis, 11 receiving cancer therapy including pulmonary resection, and 13 with postpneumonic empyema. Omentopexy, lung resection and thoracoscopic surgery were performed in ten, five and four patients respectively. Poor results of treatment were observed in two of the patients with post-tuberculous empyema, and three of the patients treated for cancer died from recurrence. The other 40 patients remained symptom free. A postoperative improvement in quality of life was revealed by exercise testing rather than by static spirometry. Optimal therapy for chronic empyema requires selection of the most appropriate first and staged procedures for each patient. Moreover, lung resection should be minimal. In a critical state, open thoracostomy must be performed as the first procedure, while omentopexy or thoracoplasty should be restricted to selected patients. Dead space and minor air leakage may safely be left alone. A video-assisted procedure may be selected for postpneumonia empyema.

General surgery

Whole blood chemiluminescence, which allows the evaluation of both oxygen radical release by phagocytes and serum opsonin activity using very small amounts of blood, is considered to be a useful means of assessing host defence against infection¹⁴. Some authors measured the whole blood chemiluminescence in 59 patients before and after open surgery (by laparotomy) for gastrointestinal disease. Early postoperative infection was detected in 12 (20 per cent) of the 59 patients. These 12 patients all had significantly higher white blood cell counts than the non-infected patients on the third and subsequent days after surgery ($P < 0.01$). The peak chemiluminescence in the group with early postoperative infections was also sig-

nificantly higher than that in the non-infected group on the day of surgery ($P < 0.0001$), 1 day after surgery ($P < 0.0001$) and 3 days after surgery ($P < 0.01$). Whole blood chemiluminescence may therefore be a useful method for the early detection of postoperative infection in the future.

To identify genetic prognostic markers for breast cancer, loss of heterozygosity (LOH) at 11q, 16q, 17p, 17q and 18q, as well as amplification of the *ERBB2*, *INT2* and *MYC* genes, was analysed in 131 patients with breast carcinoma, 49 of whom had lymph node involvement but none of whom had distant metastases¹⁵. Among the several chromosome arms tested, LOH at 17q correlated with lymph node metastasis. Amplification of the *ERBB2*, *MYC* and *INT2* genes was found more frequently in tumours from patients with lymph node metastases than in tumours from those without lymph node metastases. Univariate analysis demonstrated that LOH at 17q and *INT2* amplification were factors influencing disease-free survival. A multivariate analysis was performed on 89 tumours in which evaluation for both LOH at 17q and *INT2* amplification was possible; the results showed that patients who had tumours with these genetic changes were more likely to have a poor prognosis. The findings of this study suggest that investigating genetic changes, in addition to conventional clinicopathological factors, may contribute to defining groups of patients with breast cancer with differences in prognosis.

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Hypertonic saline attenuates end-organ damage in an experimental model of acute pancreatitis

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Background: Hypertonic saline (HTS) has been noted previously to reduce neutrophil activation. The aim of this study was to elucidate the effect of hypertonic resuscitation on the development of end-organ damage in an animal model of pancreatitis.

Methods: Pancreatitis was induced in Sprague-Dawley rats by intraperitoneal injection of 20 per cent L-arginine. Animals were randomized into four groups (each $n=8$): controls; pancreatitis without intervention; pancreatitis plus intravenous resuscitation with normal saline (0.9 per cent sodium chloride 2 ml/kg) at 24 and 48 h; or HTS (7.5 per cent sodium chloride 2 ml/kg) at these time points. Pulmonary endothelial leakage was assessed by measurement of lung wet:dry ratios, bronchoalveolar lavage protein and myeloperoxidase activity.

Results: Animals that received HTS showed less pancreatic damage than those resuscitated with normal saline (1.0 *versus* 3.0; $P=0.04$). Lung injury scores were also significantly diminished in the HTS group (1.0 *versus* 3.5; $P=0.03$). Pulmonary neutrophil sequestration (myeloperoxidase activity 1.80 units/g) and increased endothelial permeability (bronchoalveolar lavage protein content 1287 μ g/ml) were evident in animals resuscitated with normal saline compared with HTS (1.22 units/g and 277 μ g/ml respectively; $P<0.02$).

Conclusion: HTS resuscitation results in a significant attenuation of end-organ injury following a systemic inflammatory response to severe pancreatitis.

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Introduction

Acute pancreatitis was first described by Fitz in the nineteenth century¹. Although the pathogenesis remains unclear, local and disseminated inflammation occurs, characterized by induction of the systemic inflammatory response syndrome (SIRS)^{2–4}. In extremis, the adult respiratory distress syndrome (ARDS) may develop in approximately one-third of patients^{5,6}. Overexuberant neutrophil sequestration has been implicated in this lung injury^{7–9}. The indiscriminate liberation of reactive oxygen species, enzymes (e.g. elastase), vascular endothelial growth factor and other metabolites by neutrophils causes capillary leak and end-organ damage^{10,11}. These microvascular changes are significant determinants of severity and exacerbate acinar injury^{2,3,12–14}.

Restitution of the pancreatic microcirculation early in the course of the disease may attenuate acinar necrosis. Vasoactive mediators such as nitric oxide and endothelin, perceived as protectors of microcirculatory perfusion, have

been evaluated with some success¹⁵. Resuscitation with hypertonic saline (HTS) restores the circulating volume in haemorrhagic shock and exerts favourable effects on cardiac contractility, blood pressure and peripheral tissue perfusion¹⁶. However, it also facilitates microvascular circulation by reducing endothelial cell swelling and inducing prostacyclin production^{17,18}. In addition, HTS exerts immunomodulatory effects by inhibiting neutrophil activation and restoring T cell function^{19–21}.

The aim of the present study was to elucidate the effect of HTS resuscitation on the development of end-organ damage in an animal model of acute necrotizing pancreatitis.

Materials and methods

Model of pancreatitis

Acute haemorrhagic pancreatitis was induced using a model described previously employing intraperitoneal L-argi-

nine^{22,23}. Thirty-two male Sprague–Dawley rats (weight 150–250 g) were randomized into four groups (all $n=8$). Rats in group 1 were used as controls and suffered no insult. Those in groups 2–4 received an intraperitoneal injection of L-arginine hydrochloride 500 mg per 100 g body-weight as a 20 per cent solution in sodium chloride 0.15 mol/l on day 0.

Twenty-four hours after administration of L-arginine, group 3 received an intravenous bolus of normal saline (0.9 per cent sodium chloride) 2 ml/kg via internal jugular vein cannulation under halothane anaesthesia. This was repeated at 48 h. At the same time points under similar conditions, group 4 received an intravenous bolus of HTS (7.5 per cent sodium chloride) 2 ml/kg. Groups 1 and 2 were used as controls and received neither resuscitative agent. Samples from these animals were used to provide haematological, biochemical and histological measurements. All animals were killed at 72 h. The experiment was conducted following approval by the Biological Services Unit of the university.

Biochemistry and haematology

Serum samples were collected for determination of amylase levels at 24 and 72 h using *p*-nitrophenyl-maltoheptoside as reagent (Boehringer, Mannheim, Germany). Peripheral white cell and differential neutrophil counts were determined at 72 h with a Technicon H3 automated cell counter (Bayer, New York, USA).

Histopathology

At 72 h, pancreata and the right upper lobes of the lung were excised, fixed in 10 per cent formalin, and stained with haematoxylin and eosin. Samples were assessed simultaneously by two pathologists (a trainee and a consultant) who were blinded to the experimental manipulation, using a standardized scoring system (Table 1).

Animal weight

All animals were weighed at day 0, before intraperitoneal administration of L-arginine, and at 72 h, immediately before culling under halothane anaesthesia.

Pulmonary endothelial leak and neutrophil infiltration

Pulmonary endothelial leak and oedema were assessed by measuring lung wet : dry weight ratios and bronchoalveolar lavage (BAL) protein content as described previously²⁴. Myeloperoxidase (MPO) activity was used as a marker of

Table 1 Histological injury scoring system

	Pancreas	Lung
0	Absent	Acinar loss
1	Mild	Inflammatory infiltrate
2	Moderate	Inflammatory infiltrate
3	Severe	Fibroblast proliferation
0	Absent	Adipose involvement
1	Present	Adipose involvement

Table 2 Serum amylase and animal weight

	Amylase (units/l)	Weight loss (g)
Control	4954*	0.0*
Pancreatitis	7266	35.0
Normal saline	6853	32.5
Hypertonic saline	7236	30.0

Values are median. * $P<0.01$ versus experimental groups (Mann–Whitney *U* test)

pulmonary neutrophil infiltration as described elsewhere²⁵. Protein concentrations and MPO activity were measured spectrophotometrically (MRX Microplate Reader; Dynatech Technologies, Chantilly, Virginia, USA).

Reagents

All salts, drugs and chemicals were purchased from Sigma Chemicals (St Louis, Missouri, USA).

Statistical analysis

All data are presented as median values. The Mann–Whitney *U* test was used for statistical analysis and $P<0.05$ was considered significant.

Results

Animal weight and serum amylase

Administration of intraperitoneal L-arginine resulted in a significant decrease in animal weight at 72 h compared with control animals (Table 2). However, there was no significant difference in weight loss between the pancreatitis groups ($P=0.2$). Amylase levels were significantly raised at 24 h in all experimental groups compared with control levels (Table 2).

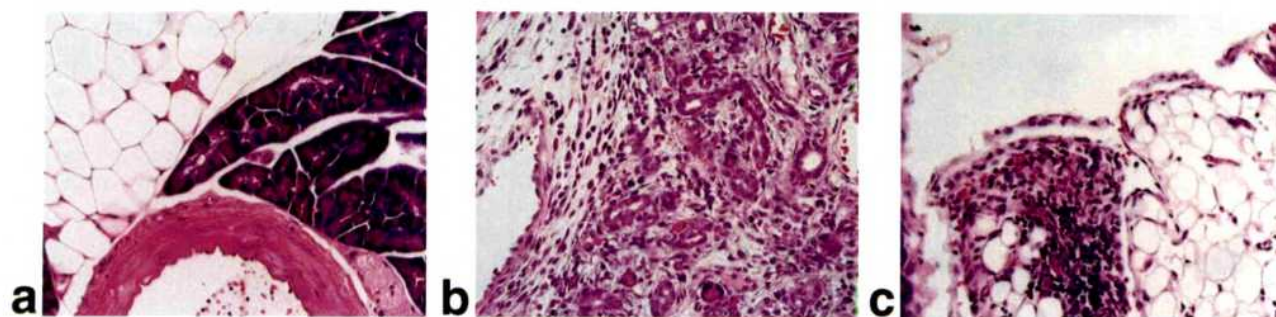


Fig. 1 Photomicrographs of rat pancreatic tissue at 72 h. **a** Control pancreas, displaying normal appearance. **b** Widespread destruction of normal architecture with focal acinar necrosis, stromal expansion with fibrosis and an acute inflammatory infiltrate in normal saline group. **c** Mixed inflammatory infiltration of adipose tissue adjacent to moderately inflamed pancreas in hypertonic saline group. (Haematoxylin and eosin stain, original magnification $\times 40$)

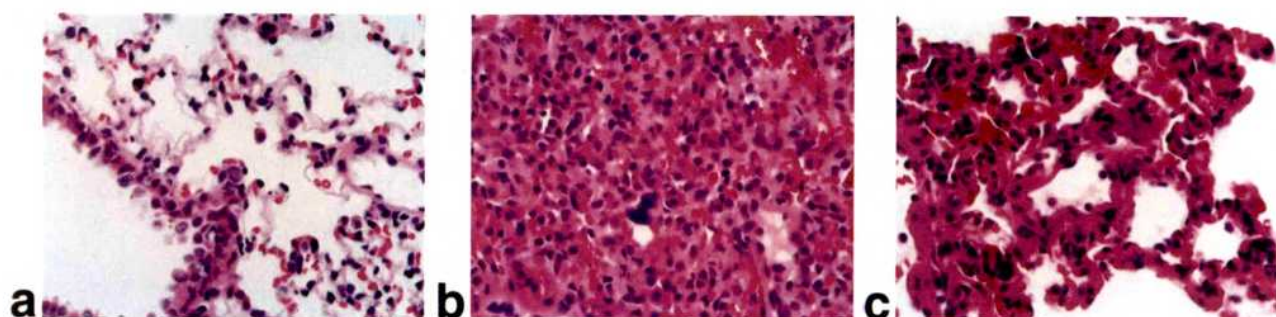


Fig. 2 Photomicrographs of rat lung tissue at 72 h. **a** Control lung displaying normal architecture. **b** Massive destruction of parenchyma with alveolar collapse, haemorrhage, oedema and a severe acute inflammatory infiltrate in normal saline group. **c** Congestion and moderate infiltration by acute inflammatory cells in hypertonic saline group. (Haematoxylin and eosin stain, original magnification $\times 40$)

Pancreatic histology

There was a visible difference in the degree of injury observed between the experimental groups. Macroscopically, the pancreatic tissue of groups 2 and 3 was markedly abnormal, and was haemorrhagic and friable compared with the mildly oedematous pancreata of animals resuscitated with HTS. Loss of normal acinar architecture, with extensive necrosis and a marked inflammatory infiltrate, evident in groups 2 and 3, was less marked in the HTS-treated animals (*Fig. 1*); the pancreatic injury scores in these animals were correspondingly lower (*Table 3*). Control animals displayed normal architecture.

Lung histology

Pancreatitis resulted in significant lung injury; samples from animals subjected to pancreatitis only or to pancreatitis followed by resuscitation with normal saline exhibited marked interstitial congestion and haemorrhage (*Fig. 2*).

Table 3 Histological injury scores

	Pancreas	Lung
Control	0.0	0.0
Pancreatitis	6.0	4.5
Normal saline	3.0	3.5
Hypertonic saline	1.0*	1.0†

Values are median; results reflect confluence of opinion between pathologists. * $P = 0.04$, † $P = 0.03$ versus normal saline (Mann-Whitney U test)

Mean pulmonary injury scores were significantly improved in animals treated with HTS (*Table 3*).

Pulmonary endothelial leak

HTS improved pulmonary endothelial leak. The pulmonary oedema, enhanced neutrophil activity and raised BAL

Table 4 Pulmonary neutrophil infiltration and endothelial permeability

	MPO activity (units/g)	BAL protein content (µg/ml)	Lung wet : dry weight ratio
Control	1.26	193	2.36
Pancreatitis	1.77	2411	8.31
Normal saline	1.80	1287	8.23
Hypertonic saline	1.22*	277†	5.61‡

Values are median. MPO, myeloperoxidase; BAL, bronchoalveolar lavage.

* $P = 0.02$, † $P = 0.01$, ‡ $P = 0.04$ versus normal saline (Mann-Whitney U test)

protein content induced by pancreatitis were significantly attenuated by HTS (Table 4).

Peripheral white cell and neutrophil count

There was a significant rise in peripheral white cell count in unresuscitated animals (6.5×10^9 per litre), the normal saline group (6.4×10^9 per litre) and the HTS-resuscitated group (7.8×10^9 per litre) compared with controls (2.6×10^9 per litre) ($P < 0.01$). Interestingly, the counts in HTS-treated animals were higher than those in the other pancreatic groups ($P = 0.04$). Specifically, neutrophil fractions were increased to a greater extent in animals resuscitated with HTS (38 per cent) than in those that received normal saline (28 per cent) or non-resuscitated animals (30 per cent). However, this did not achieve statistical significance.

Discussion

Acute pancreatitis is viewed principally as being due to autodigestion of the pancreas with extravasation of proteolytic enzymes and vasoactive mediators, leading to inflammation of contiguous tissues². Entry of these noxious substances into the systemic circulation results in SIRS and multiorgan complications^{4,5}. Alteration of the pancreatic microcirculation may contribute to the severity of the inflammatory process^{15,26}. The effect of HTS administration on end-organ injury in a sterile model of pancreatitis was examined in this study.

L-arginine administration to experimental animals produced a disease process exhibiting the salient features of haemorrhagic pancreatitis, as described previously²². The degree of weight loss recorded in the experimental groups is testimony to the severity of the systemic insult. Pancreatic injury was significantly attenuated by HTS, with protection against progression to necrosis and haemorrhage. Potential mechanisms for the beneficial effects of HTS include a

reduction in endothelial cell swelling, and inhibition of leucocyte adhesion and transmigration^{17,19,21}. Altered flow velocities with an attendant improvement in perfusion may have ameliorated the pancreatic injury^{17,18}.

The sequence of events leading to lung injury in pancreatitis culminates in inappropriate neutrophil entrapment in pulmonary tissue⁷. Neutrophils are implicated in the development of increased endothelial permeability, a hallmark of ARDS⁷. The mediation of neutrophil recruitment within the lung is a consequence of complement activation, and the stimulation of adhesion molecule expression (e.g. L-selectins, β_2 integrins and intercellular adhesion molecule 1) and intra-alveolar macrophages^{27–29}. A significant reduction in pulmonary endothelial permeability and neutrophil infiltration, correlating with attenuated lung injury, was found in animals resuscitated with HTS. The increased peripheral white cell count and relative neutrophilia in these animals provide further evidence of inhibited neutrophil sequestration. Similarly, a relative neutrophilia has been noted in haemorrhagic shock models of hypertonic resuscitation²⁵.

A primary focus of earlier studies was the haemodynamic effects of small-volume resuscitation with hypertonic solutions in haemorrhagic shock¹⁶. Enhanced cardiac contractility and improved microcirculation were found with hypertonic resuscitation^{16–18,30}. More recently, the immunomodulatory influences of HTS have come under scrutiny^{19–21,25,31,32}. HTS downregulates neutrophil oxidative burst activity and adhesion molecule expression, and restores T cell function following injury^{19–21,25}. In a 'two-hit' animal model, employing haemorrhage and endotoxin (lipopolysaccharide) exposure, HTS suppressed the tendency to excessive neutrophil activation³². The mechanism(s) by which hypertonic solutions alter cellular events may be by via cytoskeleton-associated tyrosine protein kinases^{25,30–32}.

In conclusion, HTS resuscitation limits end-organ injury following a systemic inflammatory response to pancreatitis in an animal model. Therefore, the benefits of transient hyperosmolar resuscitation extend beyond favourable haemodynamic effects. This may extend to inappropriate proinflammatory syndromes characterized by unrestrained neutrophil sequestration in the clinical setting. A clinical trial of HTS resuscitation in severe pancreatitis is warranted.

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Chronic dysphagia following laparoscopic fundoplication

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Background: Many surgeons practise tailored laparoscopic antireflux surgery in an attempt to prevent postoperative dysphagia. The aim of this study was to determine the effect of 360° fundoplication (Nissen) or 270° fundoplication (Toupet), and the influence of abnormal oesophageal peristalsis, upon postoperative dysphagia.

Methods: This was a cohort study from three tertiary referral centres, using dysphagia before laparoscopic fundoplication and 1 year after operation as the main outcome variable. Preoperative oesophageal manometry was performed on all patients.

Results: Some 761 patients underwent Nissen and 85 underwent Toupet fundoplication. Only 2 per cent reported severe postoperative dysphagia. There was a significant selection bias towards the Toupet operation for patients with abnormal oesophageal motility ($P < 0.001$). For patients whose oesophageal manometric findings were normal there was a significant improvement in dysphagia after Nissen fundoplication ($P = 0.02$), and no significant change following Toupet fundoplication. There was no significant change in the rate of dysphagia following either method of fundoplication amongst other subgroups in which oesophageal manometry was stratified as non-specific motor disorder, low-amplitude peristalsis, or aperistalsis.

Conclusion: A tailored approach to the degree of fundoplication is unnecessary as patients with dysmotility suffer no more dysphagia after full laparoscopic Nissen fundoplication than those who have a partial Toupet wrap.

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Introduction

Laparoscopic fundoplication for gastro-oesophageal reflux (GOR) has been employed in clinical practice since 1991¹. It has advantages over the corresponding open operation², with good long-term results^{3–5} and a low incidence of adverse sequelae⁶. Dysphagia is the complication of greatest concern, and presents in three scenarios. Mild impediment to swallowing occurs very commonly within the first 6 weeks after operation, and usually resolves spontaneously⁷. In the immediate postoperative period a small number of patients suffer acute total dysphagia¹. Finally, chronic dysphagia may persist beyond the sixth postoperative week⁷. Occasionally the dysphagia can be related to a technical complication, which is either avoidable or anatomically correctable. In some instances dysphagia is present after an apparently technically successful operation and the aetiology remains unresolved⁸. Some surgeons believe that patients with abnormal peristalsis on mano-

metric assessment constitute an 'at risk' group and should have their wrap tailored to a partial 270° Toupet fundoplication rather than a complete 360° Nissen fundoplication^{9,10}.

The aim of this study was to investigate the incidence of dysphagia in a series of patients where the surgeon was free to tailor the fundoplication to a partial wrap for patients considered to be at high risk of postoperative dysphagia.

Patients and methods

From September 1991 to August 1998, prospectively recorded data were collected for 846 consecutive patients undergoing first-time laparoscopic fundoplication for uncomplicated GOR at three tertiary referral centres: the Princess Alexandra Hospital, the Royal Brisbane Hospital and the Mater Private Hospital in Brisbane, Australia. Indications for surgery included GOR resistant to medical treatment, a desire to avoid long-term medical therapy, and

Table 1 DeMeester dysphagia scores by which patients rated swallowing symptoms

Score	Clinical details
0	None
1	Transient sensation of food sticking
2	Bolus obstruction cleared by liquids
3	Dysphagia for solids Need for dilatation Bolus obstruction requiring admission

laryngopulmonary symptoms (chronic adult-onset cough or asthma). Patients were excluded from the study if they had undergone previous antireflux surgery, or if the primary indication was a large paraoesophageal or mixed hiatus hernia.

GOR (DeMeester) symptom scores¹¹ were used by patients to rate their swallowing symptoms on a scale of 0–3 before laparoscopic fundoplication and at 1 year after operation (*Table 1*). It is generally accepted that dysphagia scores of 0 or 1 represent normality, whereas 2 or 3 represents clinically significant dysphagia.

As patients with severe heartburn may have a considerably impaired quality of life⁶, a questionnaire was designed to determine the status of patients who were cured of severe heartburn but who had exchanged this for severe dysphagia. All patient questionnaires in this study were self-administered and collected by an independent research nurse. Data were recorded on hard-copy forms and subsequently transferred to a computer database. Oesophageal manometry was undertaken in all patients using a standard station pull-through technique after a 6-h fast employing a Gaeltec (Dunvegan, Isle of Skye, UK) system incorporating three radially offset unidirectional microtransducers 5 cm apart. Oesophageal body peristalsis was measured during ten water swallows of 5 ml, 30 s apart. Peristalsis was graded as normal, non-specific motor disorder, low amplitude, or aperistalsis (*Table 2*).

Operations were performed by four surgeons, all of whom were beyond the learning curve for laparoscopic fundoplication¹². All procedures were performed with posterior crural repair following division of the short gastric vessels. Care was taken to ensure a loose floppy wrap fixed to the oesophagus over at least a 46-Fr intraoesophageal bougie. The laparoscopic Nissen fundoplication was performed using a standard technique, as described previously¹. Selected patients underwent a laparoscopic posterior partial 200–270° Toupet fundoplication¹³ if, in the opinion of the operating surgeon, a full wrap was contraindicated because of oesophageal dysmotility on preoperative testing. After operation patients were

Table 2 Stratification of oesophageal manometric findings

Type of peristalsis	Details
Normal	80 per cent or more of contractions peristaltic 80 per cent or more greater than 30 mmHg
Non-specific motor disorder	More than 20 per cent of contractions simultaneous or failed, or incomplete
Low amplitude	80 per cent or more of contractions less than 30 mmHg
Aperistalsis	

Table 3 Preoperative and postoperative dysphagia scores

	Before operation		After operation	
	Normal	Dysphagia	Normal	Dysphagia
Nissen	614	147 (19)	674	87 (11)
Toupet	68	17 (20)	71	14 (16)

Values in parentheses are percentages. Dysphagic groups represent patients with a DeMeester score of 2 or 3. There were no significant differences between the groups (Fisher's exact test)

usually discharged home on day 2 when able to tolerate a texture-modified diet.

Statistical analyses were performed on SPSS for Windows version 9.0 software (SPSS Inc., Chicago, IL, USA). As all variables in this study were categorical, cross-tabulated comparisons between the two groups were achieved by χ^2 analysis or, when appropriate, two-sided Fisher's exact test for small sample sizes. A difference was regarded as significant if $P < 0.05$.

Results

Laparoscopic Nissen fundoplication was performed in 761 patients, and 85 underwent laparoscopic Toupet fundoplication. Preoperative dysphagia scores in the two groups were well matched for this key outcome variable (*Table 3*). At 1 year after operation the number of patients in each group reporting clinically significant dysphagia was similar after either operation. Over both groups, 18 patients (2 per cent) reported severe postoperative dysphagia (DeMeester grade 3).

Sixty-four (75 per cent) of the 85 patients who underwent Toupet fundoplication had abnormal peristalsis before operation, whereas abnormal peristalsis was present in only 27 per cent (203 of 761) of the patients who had a Nissen fundoplication. This indicates a significant selection bias towards tailoring a Toupet wrap for patients with abnormal preoperative oesophageal manometric findings ($P < 0.001$).

Table 4 Preoperative *versus* postoperative dysphagia (DeMeester grade 2/3) stratified according to preoperative oesophageal manometric findings

Type of peristalsis	Nissen			<i>P</i>	Toupet			<i>P</i>
	Preop. normal	Preop. dysphagia	Total		Preop. normal	Preop. dysphagia	Total	
Normal								
Postop. normal	419	81	500		13	3	16	
Postop. dysphagia	41	17	58		5	0	5	
Total	460	98	558	0.02	18	3	21	0.55
Non-specific motor disorder								
Postop. normal	71	26	97		13	3	16	
Postop. dysphagia	11	5	16		2	1	3	
Total	82	31	113	0.8	15	4	19	0.5
Low amplitude								
Postop. normal	57	15	72		24	5	29	
Postop. dysphagia	9	3	12		2	1	3	
Total	66	18	84	0.7	26	6	32	0.5
Aperistalsis								
Postop. normal	5	0	5		7	3	10	
Postop. dysphagia	1	0	1		2	1	3	
Total	6	0	6		9	4	13	1.0

Each *P* value has been derived from a separate χ^2 evaluation of a 2×2 table comparing preoperative and postoperative dysphagia for either the Nissen or Toupet wrap

Table 4 displays a statistical analysis comparing the change in dysphagia scores for either the Nissen or Toupet wrap with respect to preoperative oesophageal manometric findings graded as normal, non-specific motor disorder, low-amplitude peristalsis, or aperistalsis. For patients whose oesophageal manometry result was graded as normal, there was a significant improvement in dysphagia after Nissen fundoplication ($P=0.02$), and there was no significant change following Toupet fundoplication. Amongst patients whose preoperative oesophageal manometry result was graded as non-specific motor disorder or low-amplitude peristalsis, there was no significant change in dysphagia scores following either operation. There was also no significant change in dysphagia scores following Toupet fundoplication in aperistaltic patients. The sample size for patients with preoperative aperistalsis who had Nissen fundoplication was too small for statistical analysis; however, of the six patients, none of whom had any significant dysphagia before operation, only one developed significant dysphagia after surgery.

The questionnaire evaluating the satisfaction of patients who were cured of severe heartburn, but who developed severe dysphagia, revealed that only 27 per cent of them would definitely not have the operation again.

Discussion

Although severe postoperative dysphagia following laparoscopic fundoplication is a dreaded complication, the incidence of this problem was low (2 per cent) and, even amongst patients who exchanged severe heartburn for severe postoperative dysphagia, only 27 per cent would not go through the operation again. Persistent troublesome dysphagia can be related to obvious technical complications such as hiatal failure and proximal migration of the wrap into the chest¹⁴, or distal migration of the wrap such as the classical 'slipped Nissen'. A wrap that is created too distally, by using anterior wall of the gastric body instead of the fundus, is a technical error leading to a 'bi-lobed' stomach and subsequent dysphagia that can be corrected only by reoperation^{7,14}. Although manometrically measured lower oesophageal sphincter pressure correlates only weakly with postoperative dysphagia⁸, technical manoeuvres to avoid a tight wrap have been reported to be necessary if dysphagia is to be prevented; an excessively firm hiatal closure may result in dysphagia^{15,16}, if the use of a large-calibre intraluminal bougie is omitted or a long wrap constructed¹⁵. Inadequate fundal mobilization, including failure to divide the short gastric vessels, has been reported to be a contributory factor

to postoperative dysphagia^{7,9,15,17}. This is a controversial area and support for an alternative point of view may be garnered from the literature¹⁸. Published summaries exist documenting measures that can be taken to avoid these technical complications¹⁹.

More problematic are the patients who suffer dysphagia after an apparently technically successful operation, and in these instances the mechanism remains less clear⁸. Abnormal illness behaviour contributes to patient satisfaction with the outcome of laparoscopic Nissen fundoplication, and could facilitate self-assessment of untoward results in some patients²⁰.

There is a strong belief held by some surgeons that patients at high risk of postoperative dysphagia, such as those with abnormal peristalsis on manometric assessment, should have their wrap tailored to a partial 270° Toupet fundoplication rather than the complete 360° Nissen fundoplication^{9,10,21}. This conjecture assumes that the Nissen fundoplication worsens dysphagia in patients with dysmotility, and that the Toupet fundoplication is comparatively superior to the Nissen operation in reducing the incidence of dysphagia in high-risk patients. Objective evidence is accumulating that refutes both assumptions. Mughal *et al.*²² examined patients following open Nissen fundoplication and demonstrated that those with a severe propulsive disorder did not have a significantly different clinical outcome from the group overall. Baigrie *et al.*²³ studied patients prospectively following laparoscopic Nissen fundoplication, amongst whom 54 per cent with disordered peristalsis had troublesome dysphagia before operation, but only 6 per cent had persistence of this symptom at 1 year. Mathew *et al.*⁸ studied the manometric findings of patients who underwent laparoscopic Nissen fundoplication both before and after operation, and could discover no correlation between clinical outcome and peristaltic success. Beckingham *et al.*²⁴ studied 81 patients undergoing laparoscopic Nissen fundoplication, dividing the group into 48 patients with normal motility and 33 with oesophageal dysmotility by accepted criteria. No significant differences in dysphagia between the two groups were observed by comparisons made before or after operation, at 3 months and at 1 year.

The results of the present study of a considerably larger cohort of patients with 1-year follow-up indicate that significant dysphagia is improved following the laparoscopic Nissen operation. Furthermore, when patients with dysmotility are stratified according to defined criteria for motility disorders, they are not disadvantaged by post-operative dysphagia compared with patients with normal motility. The only possible caveat is in the very small minority of patients with complete aperistalsis, in whom it was not possible to draw comparisons because of the small

sample size. Only one of six patients in this group developed significant postoperative dysphagia. In the Nottingham study all five patients with aperistalsis before operation had an improvement in motility following laparoscopic Nissen fundoplication²⁴.

With respect to the purported advantages of Toupet fundoplication over the Nissen operation, randomized studies have repeatedly failed to confirm long-term differences in the incidence or severity of dysphagia^{8,25}, even when patients with dysmotility were specifically assessed²⁶. However, all of these randomized trials were conducted in the era of open fundoplication, and the data reported here provide the strongest evidence to date suggesting that the same results will be achieved for laparoscopic fundoplication.

These results suggest that a tailored approach is unnecessary as patients with dysmotility suffer no more dysphagia after a full laparoscopic Nissen fundoplication than those who have a partial wrap.

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Interleukin 10-deficient colitis: new similarities to human inflammatory bowel disease

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Background: Interleukin (IL) 10 is a potent anti-inflammatory cytokine. Disruption of the IL-10 gene in C57/Black6 mice results in enterocolitis in the presence of intestinal bacteria. This study investigated gut mucosal barrier function sequentially during the development of colitis in this model.

Methods: Animals were bred in specific pathogen-free conditions and transferred to conventional housing at 4 weeks. Mice were evaluated at 6, 8, 10, 12, 14 and 15 weeks of age. Barrier function was assessed by measuring intestinal permeability and antibody response to systemic endotoxaemia (antibody to the core glycolipid region of lipopolysaccharide; EndoCAB). Colons were harvested and a histological injury score (HIS) was calculated.

Results: The HIS increased progressively until 12 weeks, with an associated increase in intestinal permeability, and immunoglobulin (Ig) M and IgG EndoCAB. The HIS correlated positively with both intestinal permeability and IgM and IgG EndoCAB. Intestinal permeability showed a positive correlation with EndoCAB.

Conclusion: IL-10 knockout mice develop colitis with an associated disturbance in gut mucosal barrier function, as measured by increased permeability and endotoxaemia. The colitis found in the IL-10 knockout mouse shares these histological, physiological and biochemical features with human inflammatory bowel disease and is therefore suitable for therapeutic trials. A measure of endotoxaemia correlated directly with intestinal permeability in this model.

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Introduction

Despite extensive research into Crohn's disease and ulcerative colitis the aetiology, pathogenesis and natural history of inflammatory bowel disease (IBD) remain poorly understood. There is evidence that genetic, environmental and immunological factors are involved in the disease process¹. Recently there has been renewed interest in the role played by luminal factors, most notably enteric bacteria, in the onset and perpetuation of the disease².

The complexity of IBD is not easily reproduced in simple laboratory models such as tissue culture systems³. Experimental animal models allow study of the immunological and genetic components of colonic inflammation and their interaction³. They also provide an opportunity to investigate the early stages of the disease process and to evaluate novel therapeutic agents. A suitable model should be similar to the human disease. It should arise spontaneously, have the same aetiology and pathogenesis as human IBD, have a similar spectrum and

be responsive to similar therapeutic agents⁴. While animal models provide information relevant to human disease and complement studies in IBD, they can never replace clinical trials.

A number of genetically engineered spontaneous models of colitis have been developed recently which have several features in common with human Crohn's disease or ulcerative colitis^{5–7}. Kühn *et al.*⁸ developed one of these models in 1993. Using gene targeting they developed the interleukin (IL) 10 gene-deficient mouse. Unless kept in germ-free conditions these animals develop chronic transmural enterocolitis with mucosal hyperplasia, granulomas, increased numbers of crypt cells, pseudopolyp formation, inflammatory cell response and aberrant expression of major histocompatibility complex class II antigens on the intestinal epithelia⁸. This inflammation has been well characterized in several strains of mouse in which the IL-10 gene has been deleted⁹. It bears a close resemblance to human Crohn's disease in particular, although they cannot be equated.

Disturbed gut mucosal barrier function is a feature of human IBD with increased gut permeability¹⁰ and endotoxaemia¹¹. The purpose of this study was to investigate gut barrier function in the IL-10 knockout mouse model of colitis and its relationship to colonic inflammation.

Materials and methods

The study was carried out under the regulations of the United Kingdom Animals (Scientific Procedures) Act 1986. Breeding pairs of IL-10 knockout mice from a C57/Black6 background were obtained from Bantin and Kingham (Hull, UK). These animals had been born, raised and transported in specific pathogen-free (SPF) conditions. Breeding pairs were housed in SPF isolators (Mordun, Edinburgh, UK). Litters born in the isolator were weaned at approximately 3 weeks of age and then transferred to conventional conditions at 4 weeks old. Mice were weighed twice weekly from this time. Six animals were studied at 6, 8, 10, 12, 14 and 15 weeks of age.

Intestinal permeability was assessed with the technique described by Ryan *et al.*¹², using carbon-14-radiolabelled polyethylene glycol 4000 (PEG). Radiolabelled PEG solution (0.1 ml) was administered to each animal by gavage tube 24 h before termination of the experiment. Immediately thereafter the animals were anaesthetized using Hypnorm (Janssen, Beerse, Belgium) and midazolam. A 4/0 Ethilon (Ethicon, Edinburgh, UK) circumferential anal purse-string suture was inserted to prevent mixing of liquid faeces with urine. Diuresis was induced by subcutaneous injection of 2 ml normal saline (Baxter, Belfast, UK). Animals were then placed in metabolic cages and the urine was collected for 24 h. Aliquots of urine were placed in scintillation vials and 0.5 ml emulsifying scintillation fluid (Aquasafe 300 Plus; Zinsser Analytic, Maidenhead, UK) was added. The amount of radiolabelled PEG excreted in 24 h was calculated and expressed as a percentage of the total dose administered.

After collection of urine samples for 24 h the mice were anaesthetized using the method described above. Blood was collected by open cardiac puncture under aseptic conditions using a 1-ml syringe and placed in Eppendorf vials. Blood was spun at 450g for 15 min at 4°C. The supernatant serum was then pipetted into sterile cryotubes (Nunc, Roskilde, Denmark) and frozen at -70°C until assay for immunoglobulin (Ig) M and IgG antibody to the core glycolipid region of lipopolysaccharide (EndoCAB).

The peritoneal cavity was opened; the colon was dissected free of omentum and small bowel, and excised from the peritoneal reflection to the ileocaecal valve. The colon was opened longitudinally and washed free of adherent faeces. The specimen was rolled with the sigmoid

colon to the centre and the caecum to the periphery, and placed in containers of 10 per cent formyl saline until estimation of the histological score by a pathologist. Colons were embedded in paraffin, sectioned longitudinally, and stained with haematoxylin and eosin (Fig. 1). Slides were examined and assigned a histological injury score (HIS) corresponding to the severity of inflammation observed, using a validated scoring system modified from those used by Savarymuttu *et al.*¹³ and Madsen *et al.*¹⁴ (Table 1). Histological scores ranging from 0 to 15 were ascribed to each specimen.

EndoCAB concentrations were measured by the method previously described by Scott and Barclay¹⁵. Results were expressed as a percentage of pooled normal mouse serum.

Weight, intestinal permeability and EndoCAB data are expressed as mean (s.e.m.) and HIS as median (range). Differences between time points were analysed with the Kruskal-Wallis test. Thereafter the *t* test and Mann-Whitney U test were used to assess individual time points. The Pearson test was used to assess correlation. Statistical analyses were performed using the software SPSS 9.0 for Windows (SPSS, Chicago, IL, USA). *P* < 0.05 was accepted as significant.

Results

Results are summarized in Table 2. The mean (s.e.m.) weight of mice at the time of removal from the SPF conditions was 12.4(0.5) g, rising to 26.1(1.2) g at 15 weeks. There was no significant weight increase between 12 and 15 weeks of age.

IL-10 knockout mice had no evidence of macroscopic or microscopic colitis at 6 weeks. The animals developed

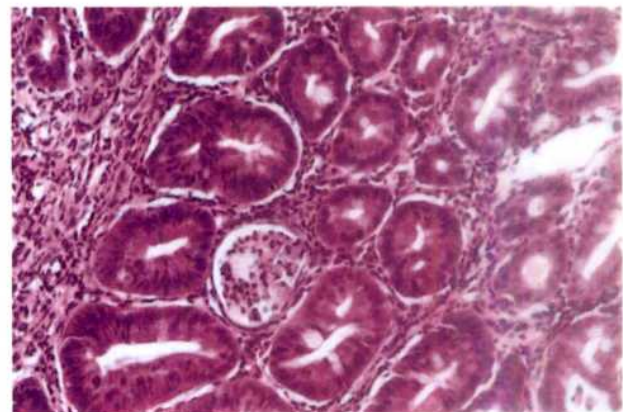


Fig. 1 High-power photomicrograph of colitis in the interleukin 10 knockout mouse showing moderately inflamed mucosa with crypt abscess formation. (Haematoxylin and eosin stain, original magnification $\times 200$)

increasing colonic inflammation, which levelled at 12 weeks of age (Fig. 2). The HIS was higher at 10, 12 and 15 weeks than at 6 weeks ($P=0.003$, $P=0.003$ and $P=0.005$ respectively). Colitis was significantly greater at 12 than at 8 or 10 weeks ($P=0.006$ and $P=0.049$ respectively). There was no change between 12 and 15 weeks, suggesting that the inflammation had reached a plateau. The scores in each of the five sections shown in Table 1 rose uniformly as the inflammation progressed.

Intestinal permeability was greater at 12, 14 and 15 weeks than at 6 weeks ($P=0.025$, $P=0.028$ and $P=0.019$ respectively). There was an increase from 8 to 12, 14 and 15 weeks ($P=0.015$, $P=0.033$ and $P=0.022$ respectively) but there was no change between 10 and 15 weeks (Fig. 3). There was

an increase in IgM and IgG EndoCAb concentrations across the time points ($P=0.003$ and $P=0.048$ respectively) (Fig. 4). The significant rise took place between 6 and 12 weeks of age for both IgM and IgG (both $P=0.023$) with no change between 12 and 15 weeks. There was a positive correlation between all variables measured using all data points (Table 3). Since each variable tended to increase until 12 weeks, the data from 12 weeks onwards were pooled in order to prove that the correlation was not simply related to time. The positive correlation remained (Table 3).

Table 1 Histological injury score

Histological appearance		Score
I	Enterocyte loss	
	Normal	0
	Loss of single cell	1
	Loss of groups of cells	2
II	Frank ulceration	3
	Crypt inflammation	
	Normal	0
	Single inflammatory cell	1
III	Cryptitis	2
	Crypt abscess	3
	Lamina propria mononuclear cells	
	Normal	0
IV	Slight increase	1
	Moderate increase	2
	Marked increase	3
	Neutrophils	
V	Normal	0
	Slight increase	1
	Moderate increase	2
	Marked increase	3
VI	Epithelial hyperplasia	
	Normal	0
	Mild	1
	Moderate	2
	Pseudopolyp	3

Maximum score 15

Table 2 Summary of results

	Age (weeks)					
	6	8	10	12	14	15
HIS*	0 (0–1)	2 (0–3)	3 (2–3)	6.5 (4–11)	5.5 (4–8)	6 (3–10)
Permeability†	0.22(0.1)	0.13(0.05)	0.69(0.31)	0.76(0.17)	1.17(0.38)	1.11(0.42)
IgM EndoCAb†	63.7(4.0)	96.1(14.7)	74.0(7.0)	124.7(19.1)	73.6(4.2)	168.1(51.4)
IgG EndoCAb†	75.6(2.2)	82.1(8.8)	82.3(5.8)	91.6(4.9)	79.2(5.1)	118.4(17.0)

Values are *median (range) or †mean(s.e.m.). HIS, histological injury score; Ig, immunoglobulin; EndoCAb, antibody to the core glycolipid region of lipopolysaccharide

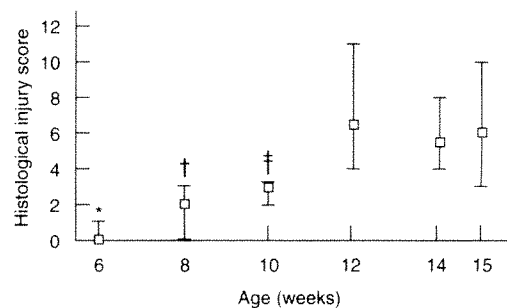


Fig. 2 Median (range) histological injury scores. $P<0.001$ (Kruskal–Wallis test). * $P=0.003$ versus 10 and 12 weeks, $P=0.005$ versus 15 weeks; † $P=0.006$ versus 12 weeks, $P=0.015$ versus 15 weeks; ‡ $P=0.049$ versus 12 weeks (Mann–Whitney U test)

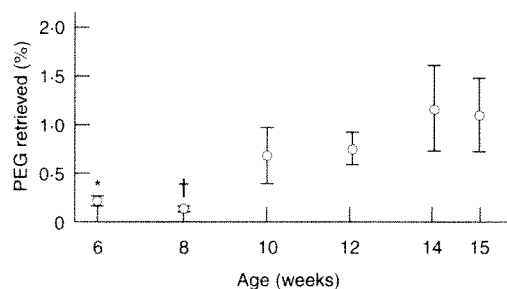


Fig. 3 Mean (s.e.m.) intestinal permeability to radiolabelled polyethylene glycol (PEG). $P=0.001$ (Kruskal–Wallis test). * $P=0.025$ versus 12 weeks, $P=0.028$ versus 14 weeks, $P=0.019$ versus 15 weeks; † $P=0.015$ versus 12 weeks, $P=0.033$ versus 14 weeks, $P=0.022$ versus 15 weeks (t test)

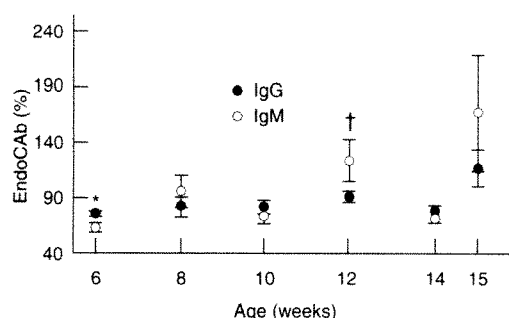


Fig. 4 Mean (s.e.m.) concentrations of immunoglobulin (Ig) G and IgM antibody to the core glycolipid region of lipopolysaccharide (EndoCAb). $P = 0.003$ (IgM), $P = 0.048$ (IgG) (Kruskal–Wallis test). * $P = 0.023$ versus 12 weeks (IgM and IgG); † $P = 0.045$ versus 10 and 14 weeks (IgM) (t test)

Table 3 Correlations between histological injury score, permeability and immunoglobulin M and G antibody to the core glycolipid region of lipopolysaccharide

	All values		12–15 weeks only	
	r^2	P	r^2	P
HIS/Permeability	0.814	<0.001	0.626	0.017
HIS/IgM EndoCAb	0.555	0.002	0.621	0.018
HIS/IgG EndoCAb	0.548	0.003	0.610	0.020
Permeability/IgM EndoCAb	0.337	0.048	0.551	0.041
Permeability/IgG EndoCAb	0.406	0.032	0.551	0.050
IgG EndoCAb/IgM EndoCAb	0.837	<0.001	0.910	<0.001

HIS, histological injury score; Ig, immunoglobulin; EndoCAb, antibody to the core glycolipid region of lipopolysaccharide

Discussion

IBD is thought to be the result of a genetically determined defect in immunosuppression resulting in an overly aggressive response to ubiquitous luminal bacterial constituents¹. IL-10 knockout mice develop chronic enterocolitis due to an aberrant immune response to normal enteric antigens¹⁶. The model is not unique in this respect. Other models such as the IL-2 knockout mouse and HLA- β 27 rat also fail to develop intestinal inflammation in germ-free conditions¹⁷. The severity of the inflammation varies depending on the strain of mouse undergoing the gene deletion, suggesting a strong inheritable component in this particular model influencing disease susceptibility⁹. The inflammation is most severe in the 129/SvEv and BALB/c strains, of moderate severity in 129 $\times$ C57/Black6 outbreds and least severe in the C57/Black6 strain⁹. This study has

confirmed that colonic inflammation in the C57/Black6 strain becomes progressively more severe as the animals age in conventional conditions. The pattern of inflammation in this model is similar to the skip lesions found in patients with Crohn's disease, and the inflammation in this model, as in human IBD, is attenuated by steroid therapy¹⁸. These findings suggest that studies using the IL-10 knockout mouse may give insight into the aetiology and pathogenesis of chronic enterocolitis, and may be useful in evaluating potential treatments for IBD.

There is evidence that patients with IBD have altered concentrations of bacteria in their faeces and associated with their intestinal mucosa. Bacteriological findings in patients with ulcerative colitis have ranged from normal to increased numbers of group D streptococci and coliforms to the presence of invasive *Escherichia coli*^{19–21}. Increased numbers of anaerobic Gram-negative and coccoid rods have been reported in patients with small bowel Crohn's disease^{22–24}, and increases in *E. coli* and *Bacteroides fragilis* in colonic Crohn's disease. In patients with active Crohn's disease, significant reductions in bifidobacteria and lactobacilli have been found, two species that are generally regarded as beneficial to the host^{25,26}. Recent work has shown that similar alterations exist in the gastrointestinal tract of IL-10 knockout mice, with an increase in colon aerobes and a contrasting decrease in *Lactobacillus* spp. adherent to the mucosa in the Sv/Ev model²⁷. This represents a further similarity between the inflammation in this model and human IBD.

Gut mucosal barrier dysfunction is a feature of IBD². Two measures of gut mucosal barrier dysfunction in IBD are systemic endotoxaemia and increased intestinal permeability. This study sequentially investigated gut mucosal barrier function in IL-10 knockout mice as inflammation progressed. Colitis was found to be associated with increased intestinal permeability to a carbon-14-radiolabelled probe. This study demonstrated a direct correlation between histological injury and gut permeability in the C57/Black6 strain of the IL-10 knockout mouse. It has recently been reported that IL-10 knockout mice on a 129/SvEv background have an increased permeability to mannitol that was present even before the onset of histological changes²⁹. The increased permeability remained as the disease progressed²⁹. Increased intestinal permeability to hydrophilic probes has been reported in patients with Crohn's disease^{30,31}. Radiolabelled probes have demonstrated that this is also the case in ulcerative colitis^{32,33}.

This study provides indirect evidence of increased systemic exposure to endotoxin as measured by increased concentrations of IgM and IgG EndoCAb in this model. There was a positive correlation between HIS and both IgM

and IgG EndoCAB. Systemic endotoxaemia has been documented repeatedly in both Crohn's disease and ulcerative colitis, and has been shown to correlate positively with clinical and biochemical activity in IBD^{34–36} and with radiological extent³⁶. Reduction in systemic endotoxaemia is associated with resolution of disease relapse³⁴. EndoCAB concentration, a more stable indicator of previous endotoxin exposure, is raised in patients with Crohn's disease and correlates positively with endotoxaemia³⁶.

This study also demonstrated a positive correlation between intestinal permeability and both IgM and IgG EndoCAB. Increased permeability has been demonstrated in association with deranged measures of gut barrier function in other animal models^{37–41}, without demonstrating a positive correlation⁴². This is the first study to demonstrate conclusively a positive correlation between intestinal permeability and endotoxaemia. This is an important finding, as measuring intestinal permeability is less invasive and more reproducible than measuring endotoxaemia. It also suggests that demonstration of increased permeability in IBD is a reliable predictor of increasing systemic exposure to intestinal bacterial antigens.

IL-10 knockout mice from the C57/Black6 background develop colitis with an associated disturbance in gut mucosal barrier function, as measured by increased permeability and endotoxaemia. These new findings are further evidence that the IL-10 knockout model has many relevant immunological, pathological and physiological similarities to human IBD. The IL-10 knockout mouse model of colitis is therefore suitable for use in trials of novel therapeutic agents that might be of benefit in IBD. Intestinal permeability measurements may prove to be a reliable indicator of systemic endotoxaemia in patients with IBD.

Acknowledgements

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Randomized clinical trial of sutured *versus* stapled closed haemorrhoidectomy

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Background: Stapled haemorrhoidectomy does not involve dissection, with its attendant potential morbidity, required to perform closed haemorrhoidectomy. This study compared haemorrhoidectomy with (sutured) and without (stapled) preliminary dissection.

Methods: Forty patients with prolapsed symptomatic haemorrhoids were randomly assigned to sutured ($n=20$) or stapled ($n=20$) haemorrhoidectomy. Preoperative assessment was by proctoscopy, sigmoidoscopy and anal manometry. Stapled and diathermy haemorrhoidectomies with wound suture were performed, and excised tissue was examined histologically. Pain scores, complications, wound healing and patient satisfaction were recorded. Follow-up was weekly for 4 weeks, and at 3 and 6 months; anal manometry was repeated at the last two visits.

Results: Postoperative resting and squeeze pressures were reduced by the stapled method at 3 months ($P=0.02$ and $P=0.03$ respectively), returning to baseline by 6 months. Stapled haemorrhoidectomy was quicker but initial access into the anus was hampered by the bulky stapler. Isolated muscle fibres were identified equally in both groups, but incontinence did not occur. The stapled technique resulted in less postoperative pain ($P=0.04$), a greater degree of satisfaction ($P=0.01$) and faster wound healing ($P<0.001$), but was more expensive. There was no significant difference in complications.

Conclusion: Despite the higher cost and difficult access, stapled haemorrhoidectomy results in less postoperative pain, faster wound healing and greater patient satisfaction than the sutured technique.

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Introduction

Ferguson's closed haemorrhoidectomy is practised widely in the USA but less frequently in the UK because of concerns that preliminary dissection exposes the haemorrhoidal wound to faecal contamination, and may result in a significant increase in wound infection, breakdown and healing by secondary intention¹. It was shown recently that stapled haemorrhoidectomy with the Proximate reloading linear cutter with safety lock-out 57-mm staple line (Ethicon, Edinburgh, UK) offers a simple, safe and effective method of closed haemorrhoidectomy through simultaneous excision and wound closure, without dissection². The aim of the present study was to compare the clinical outcome of closed haemorrhoidectomy with (sutured) and without (stapled) preliminary dissection.

Patients and methods

This study was subject to ethics committee approval and informed written consent. Forty consecutive patients with prolapsed symptomatic third-degree haemorrhoids were recruited from surgical outpatient clinics between March 1998 and February 1999. They were randomized to undergo sutured (group 1, $n=20$) or stapled (group 2, $n=20$) haemorrhoidectomy as inpatients. All patients were blinded before operation to the type of procedure performed as randomization (computer generated) was carried out in theatre, but this was revealed upon request at the first follow-up visit. Preoperative assessment included documentation of symptoms, proctoscopy and rigid sigmoidoscopy to exclude other pathology in the anus and rectum, and anal manometry. All patients received lactulose 10 ml three times daily for 3 days before surgery. In both groups, haemorrhoidectomy was performed under general anaesthesia with the patient in the lithotomy position; the

same anaesthetist administered all the anaesthetics and the same surgeon performed all the operations.

Sutured haemorrhoidectomy

A Parks' self-retaining retractor was positioned in the anal canal and diathermy haemorrhoidectomy commenced, following a radial elliptical incision encompassing the primary haemorrhoidal complex from just outside the anal verge, and extending to a point proximal to the dentate line. The resulting pedicle was transfixed with chromic catgut and the wound closed with a continuous over-and-over technique terminating at the external skin edge^{3,4}. The anal canal was then lightly packed with gauze dressing impregnated with soft paraffin (Paranet, Vernon-Carus, Preston, UK) soaked in 2 per cent lignocaine gel, which was removed the following morning.

Stapled haemorrhoidectomy

Stapled haemorrhoidectomy with the Proximate reloading linear cutter was performed as described previously². At the end of the procedure, the anal canal was lightly packed as in the sutured group.

Data collection

The duration of operation was measured by an independent observer, and the ease of operation was recorded by the surgeon using a linear analogue scale from zero to 10 (0, easiest; 10, most difficult). Excised haemorrhoids were examined histologically to determine inclusion of the anal sphincter muscle. Postoperative parenteral analgesia administered was recorded. On discharge, patients received a combination of oral analgesics (diclofenac sodium 50 mg three times daily and two co-dydramol tablets four times daily), 2 per cent lignocaine gel for topical application as required and laxatives (lactulose 10 ml three times daily and Sennoside (Reckitt and Colman Products, Hull, UK) one tablet daily) for 7 days. Patients were asked to document all analgesics used and perceived pain for 7 consecutive days after surgery, using a scale from zero to 10 (0, no pain; 10, severest form of pain), which was also adapted to measure overall level of satisfaction (0, least; 10, greatest). Follow-up was initially weekly for 4 weeks, and then at 3 and 6 months. Anal manometry was repeated at the 3- and 6-month review.

Statistical analysis

The healing rate in the sutured group was assumed to be 50 per cent, and an improvement to 82 per cent in the stapled group would be significant at the 5 per cent level with a

power of 80 per cent, in a prospective sample size of 40 patients in each group. The Mann-Whitney *U* test was used to establish the difference between groups 1 and 2 with respect to the duration and ease of operation, postoperative pain, overall satisfaction, and preoperative and postoperative resting and squeeze anal pressures. Comparison of complication, wound healing and hospital readmission rates was with Fisher's exact test.

Results

There were 12 men and eight women, of mean (range) age 48.6 (28–76) years, and 13 men and seven women, of mean age 48.6 (28–67) years, in groups 1 and 2 respectively. There was no significant difference in the number of patients in either group with pain (11), bleeding (18), prolapse (17) and discharge (eight). Two patients in the sutured and one in the stapled group were incontinent to liquid stool before operation, but had haemorrhoids sufficiently symptomatic to warrant surgery and did not suffer exacerbation of their symptoms at 6-month follow-up.

The mean (range) preadmission and postoperative resting and squeeze manometric pressures in the sutured and stapled groups are shown in *Table 1*. No significant difference was demonstrated in the preoperative resting and squeeze pressures between the two groups ($P=0.25$ and $P=0.11$ respectively). The median (range) duration of operation in the sutured and stapled groups was 40 (15–65) and 21 (14–60) min respectively ($P=0.03$), but there was no difference in the overall ease of operation score: 4.5 (2–9) versus 3.5 (2–9) ($P=0.1$). The surgeon had difficulty gaining access into the anal canal in eight patients owing to the presence of very large confluent haemorrhoids and the bulky stapling device.

Skeletal muscle fibres (group 1, four patients; group 2, none) and smooth muscle fibres (group 1, seven; group 2, 13) were identified histologically, but this did not result in incontinence. In the immediate postoperative period, 11 patients in the sutured and nine in the stapled group

Table 1 Median preoperative and postoperative resting and squeeze pressures in the sutured and stapled groups

	Preoperative	Postoperative	<i>P</i> *
Sutured			
Resting pressure	63 (20–113)	64 (19–114)	0.59
Squeeze pressure	143 (32–400)	159 (30–118)	0.76
Stapled			
Resting pressure	75 (30–118)	58 (23–89)	0.02
Squeeze pressure	218 (98–387)	154 (76–317)	0.03

Values are mean (range). *Mann-Whitney *U* test

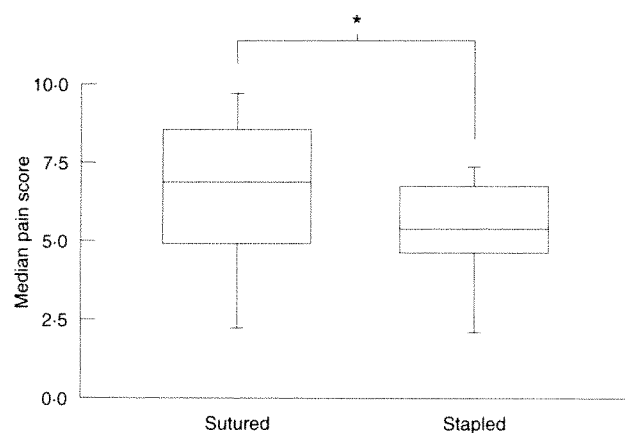


Fig. 1 Pain scores after sutured and stapled haemorrhoidectomy. * $P=0.04$ (Mann-Whitney U test)

required morphine injection ($P=0.75$), and the median (range) satisfaction scores for the corresponding groups were 1 (0–2) and 2 (0–5) ($P=0.01$). The distribution of pain scores after sutured and stapled haemorrhoidectomy is shown in Fig. 1; two patients in group 1 and one in group 2 were readmitted following discharge. The median (range) number of oral analgesics consumed by the sutured group was significantly greater than that in the stapled group: 63 (55–77) and 49 (43–77) respectively ($P<0.05$). There was no significant difference between the groups in early (group 1: one patient with urinary retention, one with faecal impaction, and one with retention and impaction; group 2: one with nausea and vomiting and one with bleeding) or late (group 1: three with anal stenosis and two with incontinence to flatus; group 2: two with incontinence to flatus and two with anal fissure) complications; however, wounds healed faster in group 2 ($P<0.001$) (Table 2). The cost of each stapling device with two reloading cartridges was £241 per patient.

Discussion

This study was designed to investigate whether closed haemorrhoidectomy by the stapled technique confers any clinical advantage over the sutured method. Stapled haemorrhoidectomy involves simultaneous excision of haemorrhoids and wound closure, without dissection, thereby eliminating potential contamination of the anal wound².

Preoperative resting and squeeze anal pressures were similar in both groups, but were reduced after operation in the stapled group. This disparity in preoperative and postoperative manometric values was significant, and may be attributed to the combined effect of haemorrhoidectomy and generous anal sphincter stretch with the Parks'

Table 2 Comparison of wound healing after sutured and stapled haemorrhoidectomy

	Wounds healed			
	2 weeks	3 weeks	4 weeks	> 4 weeks
Sutured	0	5	4	11
Stapled	8	1	5	6

$P<0.001$ (stapled versus sutured, Fisher's exact test)

retractor^{5,6}, which was necessary to accommodate the relatively bulky stapling device. Predictably, the stapled operation was quicker to perform as it avoids dissection, and achieves haemorrhoid excision, with simultaneous wound closure and near-perfect haemostasis, after firing the device. However, it emerged from this study that preliminary dissection, ligation of the vascular pedicle, securing haemostasis from the bleeding mucosal edges (despite use of the cutting diathermy) and wound closure added to the duration of the sutured operation. The surgeon occasionally encountered difficulty in manoeuvring the stapling device in the anal canal with especially large confluent haemorrhoids, which might explain why there was no significant difference in perception of ease of operation between the groups.

Histological identification of skeletal muscle fibres in four excised specimens in the sutured group seemed alarming, but is not unusual in that the subcutaneous external sphincter muscle may occupy the terminal portion of the anal canal⁷. Moreover, it was not entirely surprising that smooth muscle fibres were demonstrated in the excised specimens in both groups because they cross the plane of resection from the internal sphincter to the anal cushion⁸. There remains controversy about whether these smooth muscle fibres are indeed subepithelial in origin or originate from the internal anal sphincter, as they are difficult to distinguish histologically. An important deduction from this observation is that the histological presence of muscle fibres in excised haemorrhoidal tissue by the sutured or stapled technique does not necessarily render the patient incontinent of faeces, but may result in transient incontinence of flatus. Normal continence to flatus returned in all four patients (two sutured, two stapled) within 3 months of surgery, possibly owing to compensation from the external sphincter following haemorrhoidectomy⁵.

In the immediate postoperative period, fewer patients in the stapled group required parenteral analgesics; patients in this group used fewer oral analgesics, suffered significantly less postoperative pain and expressed a higher level of

satisfaction overall. The stapled operation incurred extra expense attributable to the cost of the device and two reloading cartridges; in some patients with very large confluent haemorrhoids, an additional cartridge was necessary. None the less, this initial cost might be offset by direct savings made from a reduction in the total amount of postoperative analgesia required, and through indirect gains from the faster rate of wound healing after stapled haemorrhoidectomy.

Proponents of the cutting diathermy method suggest a theoretical advantage in postoperative pain relief through the induction of a third-degree burn, but the findings from this study indicate that areas denuded of epithelium following dissection may still contribute to painful anal spasm and sepsis, even after wound closure^{9,10}. It would appear from the data presented that the potential avoidance of wound contamination by the stapled technique aided faster wound healing. However, no significant difference in the overall complication and readmission rates was demonstrated between sutured and stapled haemorrhoidectomy.

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Causes of re-recurrence after polytetrafluoroethylene patch saphenoplasty for recurrent varicose veins

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Background: The aim of this study was to determine whether a polytetrafluoroethylene (PTFE) patch sutured over the religated saphenofemoral junction could reduce the rate of recurrence after operation for recurrent varicose veins.

Methods: Fifty patients who had surgery for recurrent long saphenous incompetence (81 legs) had a small PTFE patch sutured over the religated saphenofemoral junction. There were no major complications following surgery. Three patients had a wound infection or delayed healing. All patients were invited for clinical examination and duplex imaging at a median of 19 (range 6–39) months after operation.

Results: Some 38 of 43 patients (70 legs) remained satisfied with the results of surgery; 16 (23 per cent) of 70 legs had visible veins on inspection and eight of these (11 per cent) involved symptomatic recurrence. Duplex imaging showed that recurrence was due to saphenofemoral junction incompetence in ten legs; two appeared to have a major groin connection but the other eight appeared to have neovascularization. Other causes were thigh perforator reflux (three legs) and cross-groin collaterals (three). Eleven of the 16 legs with recurrence had varicography but in two the procedure was a technical failure. Two legs had evidence of a significant connection (more than 3 mm) and two a minor connection (less than 3 mm) to the femoral vein at the level of the PTFE patch, but in the remainder recurrence was due to upper thigh perforating veins. There was good concordance between duplex imaging and varicography.

Conclusion: PTFE patch saphenoplasty appears to be safe. Although these are early results, the technique seems potentially as effective as other barrier methods that have been investigated; in ten legs (12 per cent) recurrence was attributed to failure at the level of the PTFE patch.

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Introduction

A significant part of the workload of vascular surgeons is reoperation for recurrent varicose veins; in Gloucester recurrent veins accounted for 17 per cent of varicose vein operations in the past 5 years¹. Little is known about the optimal reoperation technique in patients with symptomatic or complicated recurrent veins. Previous work in this hospital suggested that recurrence may be due to regrowth of veins at the saphenofemoral junction despite adequate saphenofemoral ligation (neovascularization)^{2,3}. The present study evaluated the use of a polytetrafluoroethylene (PTFE) patch sutured over the saphenofemoral junction to try to prevent further recurrence. Patients were reviewed clinically and with duplex imaging at least 6 months after surgery. When recurrent veins were present patients were

offered varicography for further assessment. The aim of the present investigation was to try to document the causes of recurrence after reoperative varicose vein surgery and to determine whether PTFE patch saphenoplasty was effective in preventing recurrent veins at the level of the patch.

Patients and methods

Fifty patients with symptomatic recurrent varicose veins caused by recurrent saphenofemoral incompetence (demonstrated by preoperative duplex imaging) were included in a cohort evaluation of PTFE patch saphenoplasty. Those with additional saphenopopliteal incompetence were excluded. Thirty-one patients had bilateral recurrence, resulting in a total of 81 legs treated. There were 19 men and 31 women of median age 54 (range 26–83) years.

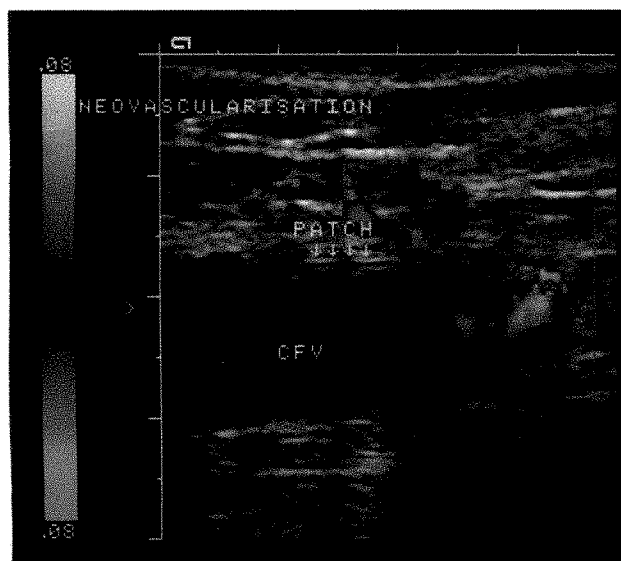


Fig. 1 Colour duplex image of a saphenofemoral junction in the region of the polytetrafluoroethylene patch showing a small recurrent vein snaking round the patch

Patch saphenoplasty

Reoperation involved the standard lateral approach to the saphenofemoral junction under general anaesthesia⁴. The junction was identified and suture ligated flush with the common femoral vein. The common femoral vein was then further exposed and cleared of tributaries over 2–3 cm. A 2 × 1-cm PTFE patch was then sutured over the ligated saphenofemoral junction using polyglycolic acid sutures, as described previously³. The groin wound was soaked in povidone-iodine before closure with polyglycolic acid sutures in two layers (subcuticular to skin). Antibiotic prophylaxis was used only in patients with distal skin ulceration. Stripping of any residual long saphenous or anterior thigh vein and stab avulsion of symptomatic venous tributaries completed the operation.

The majority of patients had inpatient surgery with a one-night hospital stay. They were reviewed in the outpatient clinic 1 month later to document complication rates. There were no major perioperative complications, but three patients developed a groin wound infection after operation that required antibiotics. All had eventual wound healing.

Follow-up

At a median of 19 (range 6–39) months after operation, all patients were invited to attend the vascular laboratory for follow-up assessment. Contact was initially made by post, and followed by a telephone call; every effort was made to

encourage participation. Those who attended completed a simple questionnaire about the results of surgery and recorded any leg symptoms. Clinical examination was performed and visible or recurrent veins were documented. All patients had duplex imaging of the leg with an 128XP/10 ultrasound scanner (Acuson, Mountain View, California, USA) and a 7–10-MHz linear array probe as described previously². Those with recurrent veins were offered diagnostic varicography to try to delineate further the cause of the recurrent veins. Varicography was carried out by a consultant radiologist. The most prominent varix was injected with iodine-based contrast agent and serial images taken using digital subtraction technology. The results were reported blind; the radiologist was not aware of previous duplex results.

Results

A median 19 (range 6–39) months after reoperative varicose vein surgery, 43 patients (70 legs) agreed to attend for review; there were 17 men and 26 women of median age 56 (range 26–83) years. Thirty-eight of 43 patients reported that they were still satisfied with the results of surgery. In the interim, no patient had required reoperative groin surgery but one had avulsion of residual superficial varicosities, one had a saphenopopliteal disconnection and one had sclerotherapy.

On examination at the time of review, superficial varicosities were visible in 16 (23 per cent) of 70 legs. In eight cases, the patients reported that the veins were symptomatic; all were, however, uncomplicated. All had venous duplex imaging. The patch was often, but not always, visualized (*Fig. 1*).

Duplex imaging

Of 70 legs imaged, 32 had incompetent flow in a residual portion of the long saphenous vein or another thigh vein, with distal connections. In almost all cases, the distal long saphenous vein was involved, usually below mid-thigh level. Serpentine tributaries were identified emanating from the ligated saphenofemoral junction in 26 groins (37 per cent). In 13, these connected to residual thigh veins to result in recurrent varicosities. In the other 13 the neovascular veins did not connect to any other thigh veins.

Deep venous disease was identified in 16 legs: in the femoral vein alone in six, in the popliteal vein alone in nine, and both in one leg. Two patients had evidence of previous deep vein thrombosis and one had saphenopopliteal incompetence. When compared with the preoperative duplex images, all but two patients had no change in the deep veins following surgery. One patient developed



Fig. 2 Varicogram showing a large tributary originating from the common femoral vein at the site of the polytetrafluoroethylene patch

evidence of non-occlusive deep vein thrombosis and one developed popliteal vein reflux of more than 2 s in the postoperative scans; both were asymptomatic.

Recurrent veins and varicography

Recurrent veins were visible in 16 legs, all in the distribution of the long saphenous vein territory. Duplex imaging suggested that in all but three legs recurrence originated at groin level; these three had large mid-thigh perforating veins. Duplex imaging suggested that in the remaining 13 legs the recurrence originated at groin level, due to neovascularization alone in five, cross-groin collateral veins in three and neovascularization with cross-groin collaterals in three. Two patients had a large (more than 3 mm) reconnection at the saphenofemoral junction (*Fig. 2*). Recurrence was more likely in patients with deep venous incompetence (six of 16) than in those with normal deep veins (ten of 54).

All 16 patients with recurrence were offered varicography. Varicography was attempted in 11 legs but a vein could



Fig. 3 Varicogram showing multiple small tributaries originating from the common femoral vein at, and just below, the site of the polytetrafluoroethylene patch

not be cannulated in two. There were two major and two minor reconnections at, or near, the PTFE patch. In the remainder, multiple connections were seen at varying levels from the common femoral vein to any residual thigh vein (*Fig. 3*).

In the nine patients who had both duplex imaging and varicography, concordance between the results was good. Both the patients thought to have a mid-thigh perforating vein on duplex imaging had this confirmed by varicography. Of the remaining seven legs thought to have groin recurrence on duplex, varicography confirmed two major (more than 3 mm) and three minor (less than 3 mm) reconnections at, or near, the level of the PTFE patch. The other three all had small tributaries, often multiple, connecting recurrent veins to the upper common femoral vein below the level of the PTFE patch. Duplex imaging and varicography agreed on the principal site of recurrence in all legs but varicography often revealed multiple connections. Both agreed that failure at the level of the PTFE patch occurred in four legs (6 per cent), two major and two minor. A further six patients who had duplex imaging alone could also have had failure at patch level resulting in an overall rate of ten (12 per cent) of 81.

Discussion

Little is known about the results of surgery for recurrent varicose veins. It is, however, generally agreed that recurrent veins represent a significant proportion of the workload of a vascular department, and that the operation is technically demanding and complicated⁵. In this and other studies, recurrence after reoperative varicose vein surgery was relatively frequent, and the principal site of recurrence was at groin level⁶. There is much debate about the reason for failure of varicose vein surgery at this site. One possibility is the growth of new veins from the ligated end of the saphenofemoral junction (neovascularization)⁷. Alternatively, these veins may simply be the result of dilatation of pre-existing collateral veins. It is clear, however, that the groin is the site of failure in most operations for long saphenous varicose veins, and it is there that any remedial measure should be focused.

Several surgical techniques have been shown to affect the rates of recurrence after surgery for primary long saphenous varicose veins, including formal flush saphenofemoral disconnection and stripping the long saphenous vein in the thigh^{8,9}. Sheppard¹⁰ introduced the concept of creating a barrier at the level of the groin to try to prevent reconnection. He suggested using a flap of pectineus fascia sutured over the ligated saphenofemoral junction. Gibbs *et al.*⁶ investigated the use of a pectineus fascia flap in a randomized trial of patients having surgery for recurrent varicose veins, but without reducing the re-recurrence rate. Glass¹¹ suggested the use of artificial material for this purpose and was able to show that a Dacron (Du Pont, Stevenage, UK) patch at the saphenofemoral junction reduced the rate of recurrence after primary long saphenous vein surgery. This encouraged the authors to try an artificial barrier for recurrent veins. PTFE was chosen because of its safety record in arterial surgery and lack of porosity. The pilot study done in Gloucester showed that insertion of the PTFE patch was safe and that the highest incidence of groin failure was in patients with recurrent veins³. For that reason, the present study was a continuation of this experience and evaluated the causes of failure by adding varicographic assessment.

Duplex imaging and varicography are complementary techniques for the investigation of venous disease. Both identified the principal sites of recurrence in the patients investigated here. Recurrence, principally in the groin, was once again the main cause of failure (13 of 16). Varicography tended to detail more tributaries in the upper thigh and was able to locate the connection more accurately with respect to the PTFE patch than duplex imaging. Varicography failed to highlight cross-groin collaterals seen on duplex scanning in three patients, although a previous publication

suggested it was accurate for this task¹². The present investigation could not be expected to answer the debate about the origin of the recurrent veins, but a significant number originated below the saphenofemoral junction, suggesting that they were pre-existing collateral veins. It is possible, however, that the patch suppressed neovascular veins. Recurrent varicose veins caused by failure of the operation at the level of the patch were uncommon (ten (12 per cent) of 81 legs)

The results of surgery for recurrent varicose veins were a little disappointing, with a recurrence rate of 23 per cent after a median of 19 months. However, only eight legs (11 per cent) were symptomatic and none of the patients wanted further treatment at the time of review. Three patients had surgery in the interim for residual varicosities after the first reoperation. Modern results of venous surgery based on duplex imaging often seem worse than previous reports based on clinical findings. However, the results of venous surgery deteriorate with time and some of the patients in this series were studied fairly soon after operation. Repeated review will be necessary to determine the significance of neovascular veins detected at the saphenofemoral junction with no distal connection (13 (19 per cent) of 70 legs).

Duplex imaging also highlighted the significant number of legs with distal long saphenous vein incompetence despite stripping (32 (46 per cent) of 70 legs). In most patients the incompetence was in the distal long saphenous vein, at or below knee level. These were usually fed by incompetent thigh perforating veins or tributaries at mid-thigh level. However, a number of patients had incompetent veins in the upper thigh despite clear evidence of successful stripping in the operation notes. This was a surprise because the authors have documented the importance of ablating any thigh veins⁹ and made strenuous efforts to remove long saphenous and anterior thigh veins. Bifid long saphenous veins can occur, but dilatation of other existing thigh veins is an alternative explanation for this finding.

It is too soon to know whether PTFE patch saphenoplasty is effective in reducing the rate of recurrence after reoperation for varicose veins. The present study has shown that the technique is safe, but that failure at groin level is still the most significant cause of recurrent veins. This fact, supported by other trials, is justification for persisting with investigation of barrier techniques, although a larger patch may be better. Future investigation should include randomized trials of the different surgical techniques.

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Short-term results of femoropopliteal subintimal angioplasty

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Background: Subintimal angioplasty may be more successful than conventional (intraluminal) angioplasty for treatment of long femoropopliteal occlusions. This study assessed the clinical and haemodynamic outcome of subintimal angioplasty.

Methods: All patients with femoropopliteal occlusions treated by subintimal angioplasty over a 3-year period at two centres were reviewed. Clinical assessment and colour duplex imaging were carried out.

Results: Sixty-nine procedures were performed in 33 men and 33 women of median age 74 (range 47–92) years. Indications for treatment were intermittent claudication in 26 (38 per cent) and critical limb ischaemia in 43 (62 per cent). Median occlusion length was 10 (range 2–50) cm. Primary technical success was achieved in 51 occlusions (74 per cent). There were 11 complications (16 per cent); the majority were minor but surgical intervention was required in two patients (3 per cent). At 6 months the cumulative symptomatic and haemodynamic primary patency rates were 60 and 51 per cent respectively, analysed on an intention-to-treat basis. The symptomatic and haemodynamic patency rates for technically successful procedures were 80 and 77 per cent respectively.

Conclusion: In this series the short-term clinical success of subintimal angioplasty was poor because of a high incidence of reocclusion and restenosis, despite a relatively high initial technical success rate.

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Introduction

Percutaneous transluminal balloon angioplasty (PTA) is an accepted and successful method of treating chronic atherosclerotic occlusions in peripheral arteries. The results of PTA for treatment of long, chronic, femoropopliteal occlusions (greater than 10 cm) are poor in terms of both initial ability to recanalize the occlusion (primary technical success) and subsequent vessel patency^{1–7}.

Unintentional subintimal or extraluminal dissection of the arterial wall occurs frequently and usually without sequelae, even if the vessel is perforated⁸. Until recently, vessel dissection was regarded as an indication to abandon angioplasty and was a principal cause of recanalization failure. However, Bolia *et al.*⁹ and Reekers *et al.*¹⁰ observed that a successful outcome could be achieved if the false lumen (created by accidental subintimal passage) was pursued, with re-entry into the true lumen beyond the distal extent of the occlusion. Subsequent vessel patency, compared with that of previous studies of conventional PTA in the treatment of long femoropopliteal occlusions,

was favourable. Consequently, the technique of deliberate subintimal angioplasty was developed.

The purpose of the present study was to review the results of femoropopliteal subintimal angioplasty in two vascular units and to compare these with findings in previously published series.

Patients and methods

Clinical records of patients who had attempted subintimal angioplasty of the femoropopliteal arteries between November 1996 and July 1999 were reviewed retrospectively. Procedures were performed either at Derriford Hospital, Plymouth, or at Gloucestershire Royal Hospital, Gloucester, by a single consultant radiologist in each centre. Both centres used the technique as described by Bolia and Bell¹¹. Patient selection had occurred at multidisciplinary meetings involving surgeons and radiologists. Those with severe claudication were treated by subintimal angioplasty as an alternative to surgery. Patients with critical limb ischaemia were treated by subintimal angioplasty if they

were thought to be unsuitable for operation because of either co-morbidity or unfavourable disease pattern. Critical ischaemia was defined according to the second European Consensus Document on chronic critical leg ischaemia¹². Technical success was defined as recanalization with antegrade flow at the conclusion of the procedure. Peripheral run-off was documented by examining angiograms and was classified as 0–1, 2 or 3 arteries patent. Occlusion length was estimated from either duplex or digital subtraction angiographic images and recorded at the time of the procedure.

Patients were followed until they reached a clinical endpoint: death, surgical intervention (arterial bypass or major amputation) or further radiological intervention. The minimum follow-up was 1 month, the maximum 29 months. Haemodynamic patency was assessed by colour duplex imaging or angiography. Symptomatic patency required subjective improvement in claudication distance, resolution of rest pain, or healing of ulcers and minor amputations.

Discrete variables were analysed with the Pearson χ^2 test. Continuous variables were analysed with the Mann-Whitney *U* test. Patency was determined (Systat Survival package; Systat, London, UK) by means of the Kaplan-Meier method of life-table analysis¹³. All patencies are primary patencies and technical failures are included in the analysis unless otherwise stated. Haemodynamic patency, symptomatic patency and limb salvage are based on number of legs; patient survival is based on number of patients. All data were censored to last known follow-up. Statistical significance was accepted at $P < 0.05$.

Results

Femoropopliteal subintimal angioplasty was attempted in 69 legs in 33 men and 33 women. Three patients had bilateral procedures. Twenty-six legs (38 per cent) were treated for claudication and 43 (62 per cent) for critical limb ischaemia. Multiple occlusions were recanalized as a single angioplasty procedure. The median length of the occlusion was 10 (range 2–50) cm. One patient required an additional conventional angioplasty of a proximal arterial lesion. Two procedures extended into the crural vessels. Comparisons between patients treated for critical limb ischaemia and claudication are shown in *Table 1*.

Technical success and complications

Initial technical success was achieved in 51 (74 per cent) of 69 legs. Technical success was independent of symptom presentation, incidence of diabetes, smoking, hypertension and occlusion length (*Table 2*). Better initial outcomes were

Table 1 Patient data according to presentation

	Total	Critical limb ischaemia	Claudication	P†
No. of patients	66	42	24	
No. of procedures	69	43	26	
Median (range) age (years)	74 (47–92)	75 (57–92)	71 (47–89)	0.02 [§]
Smokers	18 (26)	13 (30)	5 (19)	0.30 [‡]
Diabetes	20 (29)	16 (37)	4 (15)	0.053 [‡]
Hypertension	18 (26)	13 (30)	5 (19)	0.30 [‡]
No. of patent arteries (run-off)				
0–1	36	28	8	} 0.002 [‡]
2	20	12	8	
3	13	3	10	
Median (range) occlusion length (cm)	10 (2–50)	13 (5–50)	8 (3–30)	0.12 [§]

*Values in parentheses are percentages; †Critical limb ischaemia *versus* claudication; ‡Pearson χ^2 test; §Mann-Whitney *U* test

Table 2 Technically successful and failed procedures

	Successful (n=51)	Failed (n=18)	P
Symptom			
Claudication	20 of 26 (77)	6 of 26 (23)	0.66*
Critical limb ischaemia	31 of 43 (72)	12 of 43 (28)	
Smoker			
Yes	12 of 18 (67)	6 of 18 (33)	0.42*
No	39 of 51 (76)	12 of 51 (24)	
Diabetes			
Yes	13 of 20 (65)	7 of 20 (35)	0.28*
No	38 of 49 (78)	11 of 49 (22)	
Hypertension			
Yes	12 of 18 (67)	6 of 18 (33)	0.42*
No	39 of 51 (76)	12 of 51 (24)	
Median (range) age (years)	73 (47–92)	74 (58–83)	0.32†
Median (range) occlusion length (cm)	10 (3–50)	12 (5–15)	0.87†
No. of patent arteries (run-off)			
0–1	26 of 36 (72)	10 of 36 (28)	
2	12 of 20 (60)	8 of 20 (40)	0.04*
3	13 of 13 (100)	0 (0)	

Values in parentheses are percentages unless otherwise stated. *Pearson χ^2 test; †Mann-Whitney *U* test

achieved in patients with three-vessel run-off; the majority of these were in the intermittent claudication group.

Eleven patients (16 per cent) had procedural complications, five of which occurred during or after successful procedures. Two of these patients required intervention (one surgical repair of the groin puncture site and one aspiration thrombectomy for a distal embolus). Both procedures were successful. The other six complications occurred in patients in whom recanalization was unsuccessful

ful. One procedure for critical limb ischaemia was complicated by acute thrombosis of a tibial vessel. Despite successful treatment with thrombolysis, the patient required a below-knee amputation 3 days later.

Four patients died within 30 days of treatment. All deaths occurred in patients with critical leg ischaemia and were due to cardiac causes. Two patients died after major amputation and one patient following femorodistal bypass. The fourth patient died from pneumonia with a viable limb 17 days after a successful procedure.

Clinical follow-up and patency

Clinical outcome at median clinical follow-up of 8 (range 1–29) months is summarized in *Fig. 1* (claudication group), *Fig. 2* (critical limb ischaemia group) and *Table 3*.

In the claudication group, 17 of the 24 patients reported symptomatic improvement and nine were unchanged or worse. Two patients with technically successful procedures

had deteriorated but did not require further intervention. One patient required further conventional angioplasty and one required a femoropopliteal bypass for symptomatic deterioration. There were no deaths in this group.

Nine of the 42 patients treated for critical limb ischaemia were dead at 6 months. The limb salvage rate was 21 of 41. Four patients required arterial reconstruction and six needed major amputation.

Based on an intention-to-treat basis the cumulative 6-month symptomatic and haemodynamic primary patency rates were 60 and 51 per cent respectively. The symptomatic and haemodynamic patency rates for technically successful procedures were 80 and 77 per cent respectively (*Table 3*).

Discussion

The technique of subintimal angioplasty was first reported in 1990 by Bolia *et al.*⁹. Despite increasing awareness of the method during the past decade, published results of subintimal angioplasty from centres other than Leicester, UK, have not been forthcoming. This might reflect the fact

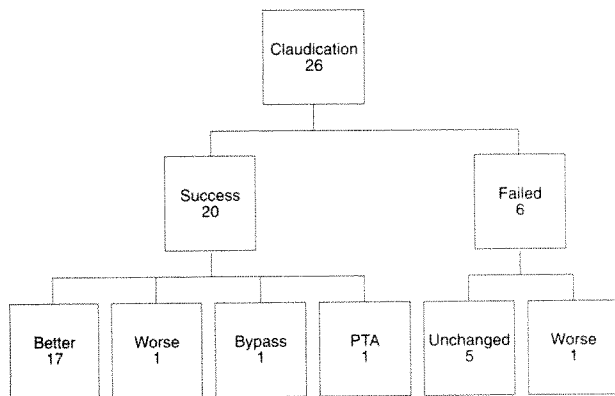


Fig. 1 Clinical outcome in claudicants at 6 months. PTA, percutaneous transluminal angioplasty

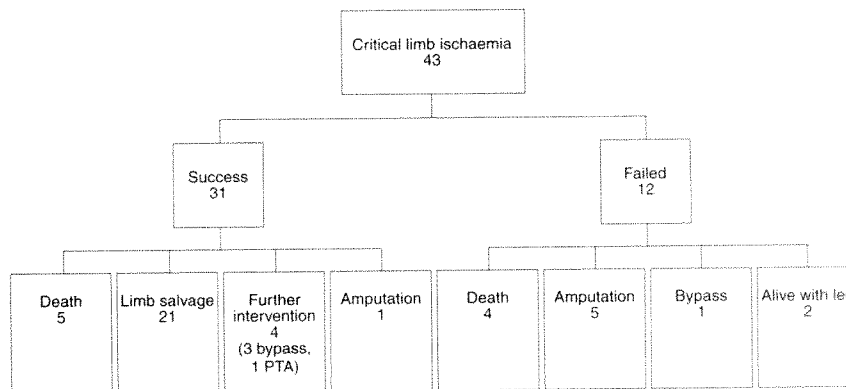


Fig. 2 Clinical outcome in patients with critical limb ischaemia at 6 months. PTA, percutaneous transluminal angioplasty

Table 3 Outcome in critical limb ischaemia and claudication

	Total	Critical limb ischaemia	Claudication
30-day mortality	4 (6)	4 (10)	0
6-month mortality	9 (14)	9 (21)	0
Intention-to-treat basis			
Symptomatic patency rate (%)	60	60	60
Haemodynamic patency rate (%)	51	50	53
Technically successful procedure			
Symptomatic patency rate (%)	80	83	75
Haemodynamic patency rate (%)	77	79	75

Values in parentheses are percentages

that the technique is associated with a long learning curve, not only in terms of radiological skills but also with regard to case selection. Alternatively, this might indicate a desire to avoid reporting results that are considerably inferior to those of the Leicester group.

Primary technical success with subintimal recanalization of the artery has been reported in 76–85 per cent of cases, with a procedure complication rate of 5 per cent^{10,14}. Haemodynamic patency rates (of successful primary procedures), determined from clinical assessment and measurement of ankle:brachial pressure index, are reported to be between 59 and 71 per cent at 1 year, and 58 per cent at 3 years. Symptomatic patency, defined as a 50 per cent improvement in claudication distance or as resolution of rest pain and/or healing of ulcers, is said to be 73 per cent at 1 year and 61 per cent at 3 years. If technical failures are included, cumulative symptomatic and haemodynamic patencies of 46 and 48 per cent can be achieved at 3 years¹⁴.

In the present study, the primary success rate of 74 per cent compared favourably with other published series of subintimal angioplasty for femoropopliteal occlusions^{10,14}. Reekers *et al.*¹⁰ reported a primary success rate of 85 per cent for femoropopliteal occlusions recanalized by subintimal angioplasty. Similarly, London *et al.*¹⁴ reported a primary success rate of 80 per cent for recanalization of femoropopliteal occlusions with a median length of 11.5 (range 2–37) cm. In both studies success was independent of length or site of occlusion.

The incidence of major complications (3 per cent) was low and similar to that of other series^{9,10,14}. Previous studies have stated that failure of subintimal angioplasty and/or complications do not reduce the chances of subsequent distal arterial bypass surgery. However, in the present series the run-off was lost in one case and, despite initial success with thrombolysis, a below-knee amputation was required; this must be regarded as a leg lost as a consequence of the procedure. Furthermore, only one of 18 patients with primary failure went on to have arterial bypass surgery.

The 6-month cumulative symptomatic (60 per cent) and haemodynamic (51 per cent) patency rates in the present study were disappointing, although the series includes the learning curves of two centres. A weakness of this retrospective study is that follow-up was not standardized. Data were censored to last known follow-up and so patency data could have been underestimated. London *et al.*¹⁴ reported haemodynamic patency rates at 12 and 36 months for all procedures to be 56 and 46 per cent respectively, and symptomatic patency rates of 58 and 48 per cent¹⁴; multiple regression analysis showed that smoking increased the risk of reocclusion 2.7 times, each additional run-off vessel reduced the risk by 0.54, and the risk increased by 1.7 for every 10 cm of occlusion length. Direct comparison is

difficult as patients in the present study were elderly (median age 74 years) and the majority (62 per cent) had critical leg ischaemia. In the series described by London *et al.*¹⁴ the median age was 68 years and only 11 per cent had critical limb ischaemia.

As a result of differences in case mix and the characteristics of lesions treated, it is impossible to make meaningful comparisons between the results of subintimal angioplasty reported thus far and other studies describing conventional PTA. However, the results of subintimal angioplasty appear favourable, both in the rate of technically successful recanalizations and subsequent vessel patency, when compared with previous studies of PTA in the treatment of long femoropopliteal occlusions. Whether centres other than those of the main proponents will be able to reproduce good outcomes following subintimal angioplasty remains to be seen. More studies using duplex imaging to determine the true haemodynamic success and long-term patency of lesions treated by subintimal angioplasty are urgently required.

The results of subintimal angioplasty still do not appear to match the patency of femoropopliteal bypass and a comparison between long-segment subintimal angioplasty and femoropopliteal bypass, examining clinical outcomes as well as quality-of-life variables, is needed. The fact that just over one-third of claudicants were unchanged or worse following subintimal angioplasty is an argument against its routine use for treating intermittent claudication. Provided the prospects of subsequent arterial bypass surgery are not unduly compromised by failed subintimal angioplasty, a reasonable strategy might be to use it as the first line of therapy in all patients with critical leg ischaemia. However, in this series only one patient underwent distal bypass following failed angioplasty. Considerably more experience from different centres is required before the role of subintimal angioplasty in this difficult group of patients can be determined. Meanwhile, a cautious approach should be adopted in which subintimal angioplasty is reserved for elderly, frail patients with critical ischaemia for whom femorodistal bypass poses a high risk or is contraindicated.

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Multicentre, randomized clinical trial of primary *versus* secondary sigmoid resection in generalized peritonitis complicating sigmoid diverticulitis

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Background: The best way to manage generalized peritonitis complicating sigmoid diverticulitis is controversial. This randomized clinical trial involved a comparison of primary resection and suture, drainage with proximal colostomy followed by secondary resection.

Methods: From January 1989 to December 1996, 105 patients of mean(s.d.) age 66(14) (range 32–91) years were randomized to undergo primary or secondary resection. The main endpoint was occurrence of generalized or localized postoperative peritonitis. The Mannheim Peritonitis Index score was calculated for each patient to check for comparability of groups.

Results: Postoperative peritonitis occurred less often after primary than secondary resection whether considering the first procedure only (one of 55 patients *versus* ten of 48; $P < 0.01$) or all procedures (one of 55 *versus* 12 of 48; $P < 0.001$). Likewise, early reoperation was performed less often following primary resection than secondary resection (two of 55 *versus* nine of 48 ($P < 0.02$) and two *versus* 11 ($P < 0.01$)), leading to a shorter median first hospital stay for patients having primary resection (15 days) than for those undergoing secondary resection (24 days) ($P < 0.05$). The mortality rate did not differ significantly with regard to operative policy (primary resection 24 per cent *versus* secondary resection 19 per cent) or type of peritonitis (faeculent 27 per cent *versus* purulent 19 per cent). No patient died following a second or third procedure.

Conclusion: Primary resection is superior to secondary resection in the treatment of generalized peritonitis complicating sigmoid diverticulitis because of significantly less postoperative peritonitis, fewer reoperations and shorter hospital stay.

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Introduction

Despite the high prevalence of acute sigmoid diverticulitis, generalized peritonitis is rare¹. Thus, it is unlikely that one single surgical unit will encounter more than one or two cases of generalized peritonitis complicating sigmoid diverticulitis each year¹. The mortality rate reported in the literature ranges from 12 to 26 per cent¹ and the morbidity rate from 5 to 36 per cent^{1,2}, a possible explanation being differences in surgical management. Two radically different policies have been advocated for generalized peritonitis complicating diverticulitis: (1)

primary resection of the sigmoid colon^{3,4} and (2) suture closure of the colonic perforation whenever visible, drainage and proximal colostomy, followed by secondary resection^{1,4–6}. One review¹ comparing these two policies suggested a clear advantage for primary resection over secondary resection in terms of both immediate mortality and morbidity. On the other hand, the only prospective randomized trial published to date⁶ concluded that secondary resection was superior to primary resection, based on a significant difference in the mortality rate only in the subgroup of patients with purulent peritonitis. This conclusion, however, cannot necessarily be extended to

generalized faeculent peritonitis. In this multicentre controlled trial, morbidity and mortality rates as well as other outcome measures were compared after primary and secondary resection for generalized peritonitis complicating sigmoid diverticulitis in 103 patients over a 8-year period.

Patients and methods

Patients

From January 1989 to December 1996, 53 women and 52 men, with a mean(s.d.) age of 66(14) (range 32–91) years, in 17 surgical centres (three university hospitals, nine general hospitals and five private hospitals) participated in the study. Fifty-five patients were allocated to primary resection and 50 to secondary resection. The centres did not start or finish the study at the same time, which accounted for the variability of patient accrual per centre. The median duration of the inclusion period for all centres was 2 (range 1–7) years. Each centre included a median of 2 (range 1–4) patients per year, producing an overall median of 3 (range 2–20) patients.

Inclusion and non-inclusion criteria

All patients aged 18 years or more were eligible. Generalized peritonitis complicating diverticulitis was defined according to Hinchey's classification⁷ as the presence of generalized peritonitis either with pus (Hinchey stage III) or faeces (Hinchey stage IV) free in the peritoneal cavity. Entry criteria required visual confirmation that a perforated or inflamed sigmoid colon was the origin of the peritonitis. Patients with (a) pericolic or mesenteric abscess (Hinchey stage I) or walled-off pelvic abscess (Hinchey stage II)⁷ most often treated by antibiotics and/or percutaneous drainage²; (b) peritonitis originating from an organ other than the sigmoid colon; (c) a perforation that could be exteriorized^{1,6}; (d) a gangrenous sigmoid colon^{1,6} or intraoperative signs of carcinoma of the sigmoid¹; or (e) cirrhosis with ascites⁸ were not included.

Operative protocol

A midline incision was used. Peritoneal fluids were routinely cultured. Treatment of peritonitis included clearance of pus, faeces, exudate and as much debris and pseudomembranous material as possible, followed by lavage of the abdominal cavity with 6 litres of warm saline⁹ whenever possible (but never less than 2 litres¹⁰). Antiseptic solution such as povidone-iodine was added or not according to the surgeon's preference⁹.

Randomization

Random assignment was made in the operating room once the surgeon had opened the abdomen, cleared the abdominal cavity, checked the inclusion and non-inclusion criteria, and was sure that both surgical approaches were feasible¹⁰. Randomization was by computerized random number tables^{11,12}. Allotment was stratified according to age (65 years or more, less than 65 years)¹³ and balanced every four patients within each strata and each centre¹¹. The ethics committee of the coordinating centre approved the study and informed consent was obtained from all patients.

Operative procedures

For patients allocated to primary resection, the surgeon was free to choose one of the two following options once sigmoid resection was completed: (1) end colostomy³ or (2) primary colorectal anastomosis protected or not by a diverting colostomy^{2,14}. A second procedure was necessary either to perform colorectal anastomosis for Hartmann reversal, protected or not by a diverting colostomy, or to close the initial colostomy.

For patients allocated to secondary resection, the perforation of the sigmoid was closed by sutures whenever visible^{1,5,6,15} and feasible⁶, and a diverting colostomy was constructed. A second procedure was necessary to resect the sigmoid colon and perform the colorectal anastomosis, protected or not by a diverting colostomy.

Both surgical approaches included: (a) pelvic drainage^{4,5,15} during the first procedure; (b) clearing the rectum of faecal matter at the end of the first procedure whenever possible¹⁶; (c) removal of the distal limb of the sigmoid colon and proximal rectum when resection was performed^{13,14,17}; and (d) mobilization of the splenic flexure as required for tension-free anastomosis.

Antibiotics

Systemic antibiotics, including a third-generation cephalosporin and metronidazole, were started when the diagnosis of peritonitis was made before operation or at laparotomy. After operation, the same regimen of antibiotics was continued for 6 days unless a change was dictated by the sensitivities of identified microorganisms.

Prognostic index

Comparability of groups was assessed by the Mannheim Peritonitis Index (MPI)¹⁸. The MPI includes different weights according to whether peritonitis is purulent (6 points) or faeculent (12 points), as well as other factors such as age over 50 years (5 points), female sex (5 points),

preoperative duration of peritonitis greater than 24 h (4 points), diffuse generalized peritonitis (6 points) and organ failure (7 points) involving either kidney, lung, shock or intestinal obstruction. Patients were then analysed according to whether the MPI score was less than 21 (good prognosis) or 21 or greater (poor prognosis)¹⁹.

Endpoints

The main endpoint was the occurrence of postoperative localized or generalized peritonitis, as proposed by Krukowski and Matheson¹ and confirmed by Grunau *et al.*²⁰, and defined as the presence of pus and/or faeces at repeat operation or autopsy. Severity of postoperative peritonitis was assessed by the number of patients who needed early reoperation and the number of deaths, analysed according to the first procedure performed or to procedures as a whole¹³. Subsidiary endpoints included the occurrence of wound and extra-abdominal septic and non-septic complications. Outcome measures of quality of life¹ included the number of: (a) third procedures whenever necessary (including colostomy and/or incisional hernia closure), (b) operations needed to treat the disease, (c) definitive colostomies, and (d) postoperative days in hospital.

The postoperative period for each procedure was defined as the duration of hospital stay and the 30 days following discharge²¹. An autopsy was performed for all patients who died in hospital.

Number of patients

Based on the hope of decreasing the postoperative peritonitis rate from 25 to 5 per cent (respectively the average rate and the smallest rate found in the literature)^{1,2}, with an α risk set at 5 per cent and a β risk set at 10 per cent, in a two-tailed analysis¹¹, 49 patients were required in each group (i.e. a total of 98 patients).

Statistical analysis

Percentages were compared with the χ^2 test, whereas discrete variables were compared using Student's *t* or Mann-Whitney *U* tests as appropriate. The Mantel-Haenszel test²² was used for adjustment in the case of demographic differences. The centre effect was analysed.

Results

Of 105 randomized patients, two having secondary resection were withdrawn because of erroneous diagnosis (colonic lymphoma and perforated carcinoma of the sigmoid), leaving 55 in the primary resection group and

44 in the secondary resection group. No patients were lost to follow-up, which was at least 2 years for all surviving patients.

Comparability of groups

Preoperative and intraoperative data of patients were comparable (*Table 1*) including the MPI. However, significantly more patients underwent clearing of the rectum of faecal matter in the primary resection group (48 *versus* 25 per cent) ($P < 0.05$).

Postoperative peritonitis and morbidity

Whether analysed according to the first procedure (*Table 2*) or overall (*Table 3*), a significantly lower rate of postoperative peritonitis after primary resection ($P < 0.01$ and $P < 0.001$ respectively) led to a significantly lower early reoperation rate after primary resection ($P < 0.02$ and $P < 0.01$ respectively). All patients with postoperative peritonitis underwent reoperation, with one exception of a patient from the SR group who died before reoperation. After the second procedure (*Table 3*) there were no cases of postoperative peritonitis in the primary resection group whereas two patients having secondary resection sustained localized postoperative peritonitis, which led to two early reoperations with no death. None of the 11 patients who underwent reoperation for postoperative peritonitis in the SR group was treated by sigmoid resection. After the third procedure, postoperative peritonitis occurred in neither group (*Table 3*). The postoperative course of the three patients treated by primary resection and primary colorectal anastomosis was unremarkable; all had purulent peritonitis.

No significant differences were observed between the two groups (*Tables 2* and *3*) with regard to wound, extra-abdominal septic or non-septic complications.

Mortality

The overall mortality rate following the first procedure was 21 (95 per cent confidence interval 13–29) per cent (*Table 2*). There were no deaths following the second and third procedures (*Table 3*). Surgical policy (primary or secondary resection) did not significantly influence the mortality rate (24 *versus* 19 per cent respectively) (*Table 3*). Of the 22 patients who died, 21 had a MPI score of 21 or more. The causes of death following the first procedure are shown in *Table 4*. In patients who died, persisting postoperative peritonitis was found at autopsy less frequently in the primary resection group (one patient) than in the secondary resection group (six patients) (P not significant).

Table 1 Comparison of preoperative and intraoperative data for patients having primary or secondary resection

	Primary resection (n=55)	Secondary resection (n=48)
Mean(s.d.) age (years)	66(16)	67(13)
Age (years)		
<65	24	20
≥65	31	28
Sex ratio (M:F)	28:27	22:26
Risk factors		
Steroids for <6 months	6	4
Chemotherapy for <6 months	1	2
Pelvic radiation therapy	1	0
Apparent duration of peritonitis		
Median (range) (h)	30 (1–192)	32 (5–216)
>24 h	31	23
Organ failure*	23	22
Pulmonary	8	5
Cardiac	9	4
Renal	11	16
Septic shock	8	4
Stage of peritonitis according to Hinchey ⁷		
III (purulent)	43	34
IV (faecal)	12	14
Resection of adhering organs	4	1
Mannheim Peritonitis Index		
Mean(s.d.)	23.6(5.8)	23.1(6.6)
<21	16	12
≥21	39	36
Perforation		
Visible	46	37
Sutured	0	22
Peritoneal lavage		
Median (range) amount (litres)	6 (2–22)	6 (2–24)
<6 litres	21	17
≥6 litres	34	31
Fluid		
Saline	25	13
Povidone-iodine	22	29
Other	8	9
Clearance of the rectum of faecal matter	24	12†
Median (range) duration of procedure (min)	140 (60–780)	110 (45–360)

*One patient could have more than one complication. † $P < 0.05$, χ^2 test

Postoperative course

The median duration of hospital stay was significantly shorter in the primary resection group whether analysed according to the first procedure (15 *versus* 24 days; $P < 0.05$) (Table 2) or as a whole (27 *versus* 40 days; $P < 0.02$) (Table 3). The median time interval between the first and second procedures was significantly longer in the primary resection group than in the secondary resection group: 112 (range 52–574) *versus* 87 (range 45–255) days; $P < 0.05$) (Table 3).

In the primary resection group (Table 3), 34 patients underwent Hartmann reversal without a protecting colostomy while five remained with a definitive colostomy. Of 36 patients who underwent secondary resection, 13 had a protecting colostomy and two had a definitive colostomy.

One patient in each group refused colostomy closure, while four patients in the primary resection group and one in the secondary resection group were considered at too high a risk for colostomy closure.

There were significantly fewer third procedures in the primary resection group: four *versus* 14 ($P < 0.01$). Overall, fewer operations were performed in the primary than in the secondary resection group ($P < 0.001$) (Table 3).

Risk factors according to the first procedure

The mortality rate following the first procedure was significantly higher in patients with (Table 5): (a) age 65 years or more ($P < 0.01$), (b) MPI of 21 or more ($P < 0.01$), (c) female sex ($P < 0.02$), (d) one or more organ failures at the

Table 2 Operations, death, morbidity and duration of hospital stay according to the first procedure in patients having primary or secondary resection

	First procedure	
	Primary resection (n=55)	Secondary resection (n=44)
Operation	57	57
Lateral colostomy only	0	48
Resection and anastomosis	3	0
Protected	1	0
Not protected	2	0
Hartmann procedure	52	0
Early reoperation	2	9†
Death	13	9
Early	12	9
Late	1	0
With initial purulent peritonitis	9	6
With initial faecal peritonitis	4	3
Postoperative peritonitis	1	10‡
Generalized	1	3
Localized	0	7
Wound complications*	13	14
Abscess	11	11
Dehiscence	1	3
Hernia	10	10
Extra-abdominal septic complications*	7	11
Catheter related	0	0
Bloodborne	2	3
Urinary tract infection	3	4
Pneumonia	2	6
Extra-abdominal non-septic complications*	22	18
Cardiac failure	5	4
Respiratory failure	8	6
Stroke	6	3
Renal failure	6	5
Digestive bleeding	1	2
Miscellaneous	5	5
Median (range) postoperative duration of hospital stay (days)	15 (1–153)	24 (2–78)§

*One patient could have more than one complication † $P < 0.02$; ‡ $P < 0.01$, χ^2 test; § $P < 0.05$, Mann-Whitney U test

time of admission ($P < 0.01$), and (e) postoperative peritonitis ($P < 0.004$). Faecal peritonitis was associated with a higher mortality rate (27 *versus* 19 per cent) but this difference was not statistically significant ($P = 0.60$) (Table 5).

Postoperative peritonitis following the first procedure was significantly associated with: (a) age 65 years or more ($P < 0.05$), (b) MPI of 21 or higher ($P < 0.001$), (c) secondary resection ($P < 0.01$), and (d) faeculent peritonitis ($P < 0.06$) (Table 5).

Three protocol recommendations were not always adhered to (Table 1): lavage greater than 6 litres; in secondary resection, suture of perforation; and clearing the rectum of faecal matter. However, after statistical adjustment (Mantel-Haenszel test) none had any influence on mortality or postoperative peritonitis (Table 5). No centre effect was found.

Discussion

This study has shown that primary resection was associated with a lower rate of postoperative peritonitis, which led to fewer reoperations and a shorter hospital stay. The overall mortality rate did not differ with the surgical approach used.

The rate of postoperative peritonitis was significantly lower in the primary resection group (2 *versus* 25 per cent), especially with respect to localized peritonitis (0 *versus* 19 per cent) (Table 3). As suggested elsewhere^{7,23} one explanation for these findings may be that, although a diverting colostomy may decrease the rate of generalized peritonitis, it may not decrease the rate of localized peritonitis as better source control is obtained by primary resection^{1,23–25} than secondary resection. In contrast, the postoperative peritonitis rates after primary and secondary resection were

Table 3 Operations, death, morbidity and duration of hospital stay according to second, third and total procedures in primary and secondary resection groups

	Second procedure		Third procedure		Total including first procedure	
	Primary (n=35)	Secondary (n=36)	Primary (n=4)	Secondary (n=14)	Primary (n=55)	Secondary (n=48)
Operation	35	38	4	14	96	109*
Resection and anastomosis	0	36	0	0	3	36
Protected	0	13	0	0	1	13
Not protected	0	23	0	0	2	23
Non-protected Hartmann reversal	34	0	0	0	34	0
Closure of lateral colostomy	1	0	0	13	1	13*
Incisional hernia repair only	0	0	4	1	4	1
Early reoperation	0	2	0	0	2	11†
Death (early and/or late)	0	0	0	0	13	9
Definitive colostomy	5	2	0	0	5	2
Postoperative peritonitis	0	2	0	0	1	12*
Generalized	0	0	0	0	1	3
Localized	0	2	0	0	0	9†
Wound complications	7	9	0	0	20	23
Abscess	2	2	0	0	13	13
Dehiscence	0	0	0	0	1	3
Hernia	4	12	0	0	14	22
Extra-abdominal complications						
Septic						
No. of patients	4	1	0	0	11	12
No. of complications	6	2	0	0	13	15
Non-septic						
No. of patients	4	3	0	0	26	21
No. of complications	4	3	0	0	35	28
Median (range) length of hospital stay (days)	14 (3–64)	15 (7–45)	7 (5–9)	8 (6–16)	27 (1–180)	40 (2–102)†
Median (range) time between procedures (days)	112 (52–574)	87 (45–255)‡	120 (91–225)	70 (10–297)	121 (1–754)	123 (2–503)

* $P < 0.001$; † $P < 0.01$, χ^2 test; ‡ $P < 0.05$, Mann-Whitney U test (secondary versus primary resection)

Table 4 Causes of postoperative death following the first procedure after primary and secondary resection

	Primary resection (n=55)	Secondary resection (n=48)
Death	12	9
Persisting postoperative peritonitis	1	6‡
Generalized	1	3
Localized	0	3
Acute renal failure	0	1
Acute respiratory failure	2	2
Cardiac failure	2*	2†
Septic shock	1	2*†
Multiorgan failure	2	0
Pulmonary embolism	1	1†
Stroke	1	1
Coma	1	0
Haematoma of left psoas	1	0
Unknown at autopsy	1	1

One patient could have more than one complication leading to death.

One patient each had *persisting generalized postoperative peritonitis and

†persisting localized postoperative peritonitis at the time of death.

‡ $P < 0.1$, χ^2 test

similar in Kronborg's series⁶ (16 and 13 per cent respectively). There were, however, more patients with postoperative peritonitis following primary resection in that series⁶ (16 per cent) than in the present study (2 per cent). The reasons might be that the distal limb of the sigmoid, a potential source of infection^{13,14,17,20}, was not removed in most patients⁶ and that autopsies were not performed for all deceased patients⁶, and therefore death due to postoperative peritonitis could have been missed.

The overall mortality rate in the present study was 21 per cent, in keeping with the reported range in the literature (12–26%)^{1,13,14,23,24}. In spite of suggestions in a number of retrospective studies^{1,2,23–25}, primary resection did not decrease the mortality rate for generalized peritonitis complicating diverticulitis in this series. Possible reasons for this difference are the non-randomized nature of other studies, possible selection bias in favour of primary resection^{1,13}, an absence of a clear definition of generalized peritonitis, and failure to use a prognostic index. In this regard, the widely accepted Hinchey classification of generalized peritonitis⁷ and the MPI^{18,19} was used in the present study. MPI has been shown to be as efficient as the

Table 5 Influence of risk factors on mortality and postoperative peritonitis following the first procedure

	Mortality		Postoperative peritonitis	
	Dead (n=22)	Alive (n=81)	Present (n=11)	Absent (n=92)
Age (years)				
<65	3	41*	1	43†
≥65	19	40	10	49
Sex ratio (M:F)	6:16	45:36‡	5:6	45:47
Preoperative organ failure				
Present	16	29*	38	7
Absent	6	52	54	4
Resection				
Primary	12	43	1	54*
Secondary	10	38	10	38
Peritonitis				
Purulent	15	62	5	72§
Faecal	7	19	6	20
Perforation				
Primary resection	12	43	1	54
Secondary resection				
Not visible	1	10	9	2
Visible and sutured	5	17	5	12
Visible and not sutured	4	11	3	12
Mannheim Peritonitis Index				
Mean(s.d.)	27.2(6)	22.3(6)¶	26.2(5)	22.9(6)¶
<21	1	27*	1	65¶
≥21	21	54	10	27
Peritoneal lavage				
Primary resection				
<6 litres	2	19	0	21
≥6 litres	10	24	1	33
Secondary resection				
<6 litres	4	13	3	14
≥6 litres	6	25	7	24
Clearance of the rectum				
Primary resection				
Yes	6	18	1	23
No	6	25	0	31
Secondary resection				
Yes	5	7	2	10
No	5	31	8	28
Postoperative peritonitis				
Generalized	4	0		
Localized	3	4**		
No peritonitis	15	77		

* $P < 0.001$; † $P < 0.05$; ‡ $P < 0.02$; § $P < 0.06$; ¶ $P < 0.001$; ** $P < 0.004$. Percentages were compared with the χ^2 test; discrete variables were compared using Student's t test

Acute Physiology And Chronic Health Evaluation (APACHE) II score in predicting the short-term risk of death in patients with peritonitis^{19,20}. MPI allowed accurate assessment of the comparability of the two study groups and it correlated with the mortality rate (21 of the 22 patients who died had a MPI score of 21 or more¹⁹). Even if the lower rate of postoperative peritonitis in patients undergoing primary resection did not influence the overall mortality

rate in this series, other preoperative risk factors may have intervened to mask the effect of surgery on mortality rate. The rate of postoperative peritonitis therefore represents a better outcome measure than mortality rate for comparison between the two operative policies^{1,20}. In addition, MPI significantly predicted the onset of postoperative peritonitis, understandably because the score contains two predictive factors for morbidity: age greater than 65 years and

faeculent peritonitis (Table 5). MPI is better than APACHE II in that it predicts postoperative morbidity and well as mortality.

Kronborg⁶ found a significantly higher mortality rate after primary resection in the subgroup of patients who presented with purulent generalized peritonitis, leading to the conclusion that secondary resection of the sigmoid should be the standard treatment for generalized peritonitis complicating diverticulitis. This conclusion, however, differs from the results of several retrospective^{1,13,23} and prospective^{18,19} studies which have shown a clear trend towards lower risk in purulent peritonitis in comparison with faecal peritonitis, as in the present series (19 *versus* 27 per cent).

In the present study, 9 per cent of patients in the primary resection group remained with a permanent end colostomy, which compares favourably with the 16–30 per cent rate reported in the literature^{6,23,24,26}. In the secondary resection group, two patients (4 per cent) did not undergo a secondary resection of the sigmoid and continued with a colostomy. This also compares favourably with values reported in the literature (ranging from zero²³ to 13 per cent⁶).

The duration of hospital stay for the first procedure was significantly shorter in the primary resection group, probably because the rate of early reoperation was lower owing to less postoperative peritonitis. The difference in hospital stay increased when the total duration of hospitalization was taken into consideration because more third operations were required to treat the greater number of colostomies remaining after the second procedure in the secondary resection group^{1,6,13,24}.

Three further observations support the view that primary resection is superior to secondary resection. First, there is not always a need for temporary diverting colostomy when immediate anastomosis is performed after primary resection^{1,2,27}. Second, a colostomy is not usually required after reversal of Hartmann's procedure and, third, as shown in the present series and suggested by others^{25,28}, the interval before reversal of Hartmann's procedure can be shortened to 4 months without any mortality or postoperative peritonitis, as opposed to the 6-month delay proposed by Pearce *et al.*²⁹.

In conclusion, the results of this study confirm that in patients with generalized peritonitis complicating sigmoid diverticulitis primary resection is preferable to secondary resection because of a significantly lower overall postoperative peritonitis rate, reduced hospital stay and fewer reoperations. Patients with purulent peritonitis and/or a low surgical risk (MPI score of less than 21) may be suitable for primary resection of the sigmoid colon followed by primary colorectal anastomosis with or without a diverting colostomy^{2,25,27,28}, eventually via laparoscopy³⁰. These

suggestions remain to be tested in further multicentre controlled trials.

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Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis

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Background: Recent evidence suggests that intestinal dysfunction has a role in sustaining the systemic inflammatory response in acute pancreatitis and may be ameliorated by the introduction of enteral nutrition. This study therefore assessed the effect of early enteral nutrition on the systemic inflammatory response in patients with prognostically severe acute pancreatitis.

Methods: Patients with prognostically severe acute pancreatitis within 72 h of disease onset were randomized to receive either enteral nutrition or conventional therapy consisting of a nil-by-mouth regimen. Serum interleukin (IL) 6, soluble tumour necrosis factor receptor I (sTNFRI) and C-reactive protein (CRP) were used as markers of the inflammatory response. Intestinal function was assessed using a differential sugar permeability technique.

Results: Of 27 patients, 13 received enteral nutrition. A median of 21 (range 0–100) per cent of calorific requirements was delivered over the first 4 days by enteral nutrition. There were no significant complications of enteral nutrition. The introduction of enteral nutrition did not affect the serum concentrations of IL-6 ($P = 0.28$), sTNFRI ($P = 0.53$) or CRP ($P = 0.62$) over the first 4 days of the study. Although there were no significant differences in intestinal permeability between the two patient groups at admission ($\chi^2 = 2.33$, d.f. = 1, $P = 0.13$), by day 4 abnormal intestinal permeability occurred more frequently in patients receiving enteral nutrition ($\chi^2 = 4.94$, d.f. = 1, $P = 0.03$).

Conclusion: Early enteral nutrition did not ameliorate the inflammatory response in patients with prognostically severe acute pancreatitis. Furthermore, it did not have a beneficial effect on intestinal permeability.

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Introduction

Current paradigms of the pathophysiology of severe acute pancreatitis suggest that local pancreatic inflammation is the initiating stimulus for the development of a systemic inflammatory response which in turn promotes multiple organ failure¹. Experimental evidence suggests that intestinal dysfunction occurs early in the evolution of an attack of severe acute pancreatitis and contributes to the systemic inflammatory response^{2–4}. Whilst the precise mechanisms through which intestinal dysfunction sustains a systemic inflammatory response are not clear, evidence

exists suggesting that changes in gut barrier function are involved⁵. Direct transluminal migration of enteric bacteria from the colon to peripancreatic tissues also appears to be important in the development of infected pancreatic necrosis⁶, which may in turn sustain a host inflammatory response.

Conventional management of patients with acute pancreatitis includes the institution of a nil-by-mouth regimen, the rationale being to 'rest' the inflamed pancreas⁷. However, it is now becoming clear that luminal nutrition has a central role in the maintenance of normal gut function. There is increasing evidence that loss of luminal nutrition in

Table 1 Patient details

	Enteral nutrition (n=13)	Conventional therapy (n=14)
Sex ratio (M:F)	5:8	9:5
Age (years)	64 (26–76)	52 (23–78)
Aetiology		
Gallstone	7	3
Alcohol	4	7
Idiopathic	1	2
Other	1	2
Glasgow score ¹²	4 (1–5)	4 (1–6)
APACHE II score ¹³	10 (7–20)	12 (7–32)
Helsinki score ¹⁴	4 (1–6)	4 (0–7)
Balthazar score ¹⁵	3 (0–8)	2 (0–8)
Duration of symptoms (h)*	31 (10–72)	27 (6–68)
Duration of hospital stay (days)	10 (5–30)	10 (5–94)
End of episode Atlanta category ¹⁶		
Mild	6	5
Severe	7	9

Values are median (range). *Before admission to study. APACHE, Acute Physiology And Chronic Health Evaluation

critical illness appears to be an important factor in enterocyte and colonocyte dysfunction⁸. Moreover, studies in critical illness have demonstrated that enteral feeding maintains gut function and reduces infective complications^{9–11}.

Given this apparent conflict between the potential risks and benefits of enteral nutrition, this study evaluated early enteral nutrition in patients with predicted severe acute pancreatitis. The safety and feasibility of enteral nutrition, and the effects of enteral nutrition on intestinal barrier function and on the systemic inflammatory response, were evaluated.

Patients and methods

This study was approved by the Lothian research ethics committee. Informed consent was obtained from the patient or next of kin. Patients admitted with prognostically severe acute pancreatitis within 72 h of the onset of symptoms were eligible for study. The diagnosis of acute pancreatitis was based on a history consistent with acute pancreatitis and a serum amylase concentration greater than three times the upper limit of normal. Patients were considered to have prognostically severe acute pancreatitis if they had a Glasgow score¹² of 3 or more and/or an Acute Physiology And Chronic Health Evaluation (APACHE) II¹³ score of 7 or greater. Exclusion criteria were age below 18 years or above 80 years, pregnancy, patients already receiving nutritional support and enrolment in another clinical trial. During the period from 16 December 1996 to

1 July 1998, 156 patients were admitted with a diagnosis of acute pancreatitis. Of these patients, 51 were eligible for inclusion in the study, but 17 refused entry, three patients were entered into another trial, one patient was started on a normal diet within 24 h of admission, in one patient the diagnosis was missed initially and one patient died before entry into the trial. A total of 28 patients met the entry criteria and were randomized. One patient who met all of the entry criteria was found at laparotomy to have an acute mesenteric infarction and has therefore been excluded from the analysis. Patients were randomized to receive either conventional therapy plus early enteral nutrition or conventional therapy alone. Patients with an APACHE II score of more than 20 were randomized separately to minimize the potential for clustering of patients. The demographics of the study sample are shown in *Table 1*.

Study period

Patients were deemed to have completed the study following the introduction of a normal diet or upon completion of the tenth day.

Conventional therapy

Conventional therapy was in accordance with current British Society of Gastroenterology guidelines¹⁷. All patients were prescribed intravenous cefotaxime 2 g three times daily and metronidazole 500 mg three times daily for 4 days¹⁸. After 4 days antibiotic therapy was stopped. Further antibiotic therapy was prescribed according to bacteriological cultures or at the discretion of the treating clinician.

Nasojejunal feeding

Single-lumen 110-cm 8-Fr (Corsafe[®]; Merck, West Drayton, UK) nasojejunal feeding tubes were placed under fluoroscopic screening such that the tip of the nasojejunal feeding tube was distal to the ligament of Treitz. Tube dislodgement episodes were defined as a loss of tube position such that the tip was no longer distal to the ligament of Treitz. Routine radiological assessment of the feeding tube position was not carried out. Enteral nutrition was commenced at a rate of 25 ml/h, increasing daily by 25 ml/h until the desired caloric intake was reached¹⁹. In the presence of signs of feed intolerance the infusion rate was not increased. Jevity[®] (Abbott, Maidenhead, UK), an isotonic polymeric formula containing fibre, was used in all cases; 500 ml Jevity[®] contains 4 g protein, 3.5 g fat, 13.1 g carbohydrate and 1.4 g dietary fibre, providing 2105 kJ.

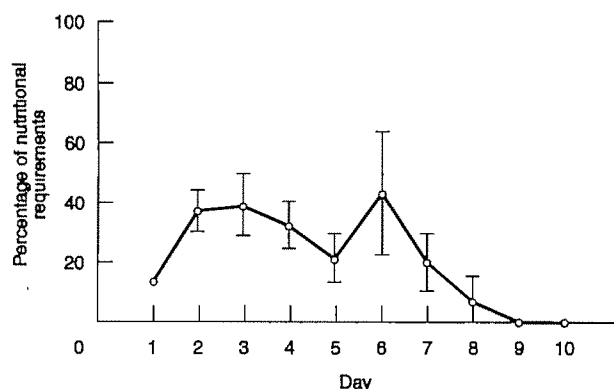


Fig. 1 Percentage of nutritional requirements delivered through enteral nutrition, calculated using the Schofield equation¹⁹. Values are mean(s.e.m.)

Study endpoints

The principal endpoint was modulation of markers of the inflammatory response in patients with predicted severe acute pancreatitis. As measures of the systemic inflammatory response the following were assayed: serum C-reactive protein (CRP), interleukin (IL) 6 and soluble TNF receptor I (sTNFRI). As an indirect measure of endotoxin exposure, serum antiendotoxin core immunoglobulin (Ig) G antibody concentrations were assayed^{5,20–22}.

Safety and tolerance of early enteral nutrition

For each 24-h period the volume of feed delivered was measured. All adverse events that were potentially attributable to enteral nutrition were recorded. Patients were assessed daily using a simple graded score: 0, no nausea; 1, nausea; and 2, vomiting.

Modulation of intestinal dysfunction

Intestinal permeability was determined using a differential sugar permeability test²³. Following a period of fasting of no less than 8 h, lactulose 5 g, L-rhamnose 1 g, sucrose 20 g and lactose 20 g were dissolved in 80 ml water and administered orally. Urine was collected for the next 5 h and sugar concentration determined by high-performance liquid chromatography. The urinary lactulose:rhamnose ratio was compared with a previously determined normal reference range. The disaccharide peak for lactulose could not be quantified if other disaccharides were present. Furthermore, excessive glycosuria prevented L-rhamnose measurement. Intestinal permeability measurements were categorized as 'normal', 'increased lactose:rhamnose ratio' and 'sucrose permeability'. Samples with glucose present were excluded from statistical analysis.

Organ dysfunction score

Organ dysfunction was quantified using the Marshall organ dysfunction scoring system²⁴.

Statistical analysis

For the majority, stated values are median (range) and statistical analysis was carried out using a non-parametric test to avoid distributional assumptions. For repeated measurements over the study period mean(s.e.m.) values are given and analysis of variance (ANOVA) was used. Statistical significance was taken at the $P=0.05$ level. Statistical analysis was carried out using the Statview 5.0 software package (SAS Institute, Cary, North Carolina, USA).

Results

Delivery of enteral nutrition

Nasojejunal tube placement was successful in 12 of 14 subjects. One patient randomized to receive enteral nutrition refused tube placement but was willing to participate in the study and therefore his results are included in the conventional therapy group. In the other patient the nasojejunal tube could not initially be passed through the pylorus but later passed spontaneously into the duodenum allowing enteral feeding. The median number of tube dislodgements was 1 (0–3) per person. Tubes remained in place for a median of 2 (1–7) days. The median number of tube placements was 1 (1–3) per person. The percentage of nutritional requirements delivered through enteral nutrition is shown in Fig. 1. The delivery of enteral nutrition in the cohort remained relatively constant, and was a median 21 (0–100) per cent of predicted requirements over the first 5 days. Over the first 4 days a median of 1.8 (0–7.3) MJ/day was delivered. After this period the majority of patients resumed a normal diet. Patients unable to establish normal diet at this stage were also less able to tolerate enteral nutrition because of established ileus, reflected in the decrease in the percentage of calorific requirement delivered enterally after day 5. By day 10 no patient was receiving artificial enteral nutrition. In three patients the volume of feed was limited by ileus. Three patients received parenteral nutrition within the study period. Parenteral nutrition was commenced on day 4 in one patient in the enteral nutrition group because of ileus and high-volume nasogastric aspirates. Two patients in the conventional group commenced parenteral nutrition on days 2 and 7, at the discretion of the treating clinician. Normal diet was reintroduced at a median of 5 (4–9) days in patients receiving enteral nutrition compared with 6 (4–10) days

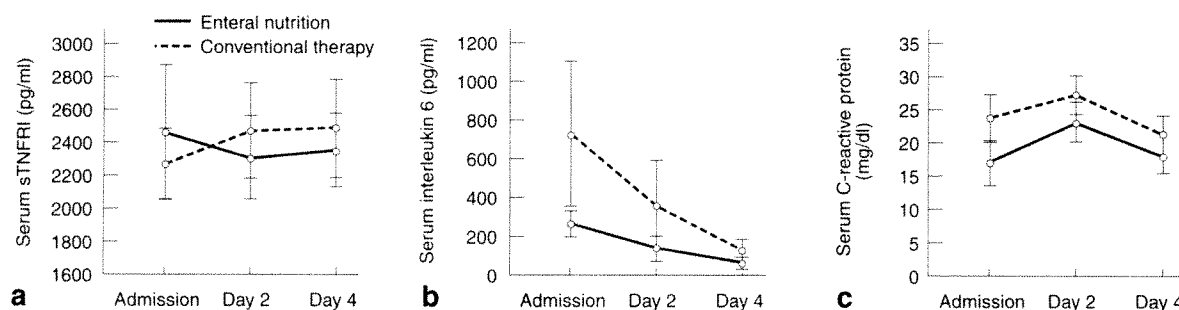


Fig. 2 Serum concentration of **a** soluble tumour necrosis factor receptor I (sTNFRI), **b** interleukin 6 and **c** C-reactive protein in patients receiving early enteral nutrition or conventional therapy. Values are mean(s.e.m.)

for the conventional group ($P=0.66$, Mann-Whitney U test).

Change in markers of the inflammatory response

As the median delay to introduction of a normal diet was 5 days and the aim of the study was to examine the effect of enteral nutrition on the systemic inflammatory response, statistical analysis was carried out on results obtained from the time of admission until day 4. Change in serum markers of the inflammatory response is seen in Fig. 2. Serum IL-6 levels fell ($P=0.01$, ANOVA) during the study period in both groups of patients. Serum sTNFRI concentration remained relatively constant ($P=0.95$, ANOVA). Serum CRP concentrations increased from admission to day 2 and then fell ($P=0.01$, ANOVA). The introduction of enteral nutrition did not affect the serum concentrations of IL-6 ($P=0.28$, ANOVA), sTNFRI ($P=0.53$, ANOVA) or CRP ($P=0.62$, ANOVA) over the first 4 days of the study. The introduction of enteral nutrition did not significantly affect concentrations of IgG antiendotoxin core antibody.

Safety and tolerance of early enteral nutrition

Although patients allocated to the enteral nutrition arm had higher nausea scores than patients in the conventional group ($P=0.03$, ANOVA), enteral nutrition did not significantly affect nausea ($P=0.23$, ANOVA) (Fig. 3). There were no major complications that were directly attributable to enteral nutrition.

Gut permeability to non-metabolized sugars

The effect of enteral nutrition on gut permeability to non-absorbable sugars is shown in Table 2. In the group receiving enteral nutrition four patients had normal intestinal permeability at admission, but by day 4 three of these individuals had developed abnormal results (in

the remainder individual sugar permeability studies were not possible). In contrast, five patients in the conventional group had abnormal results on admission and normal results on day 4.

Organ dysfunction scores

Enteral nutrition did not affect Marshall multiple organ dysfunction scores ($P=0.52$, ANOVA).

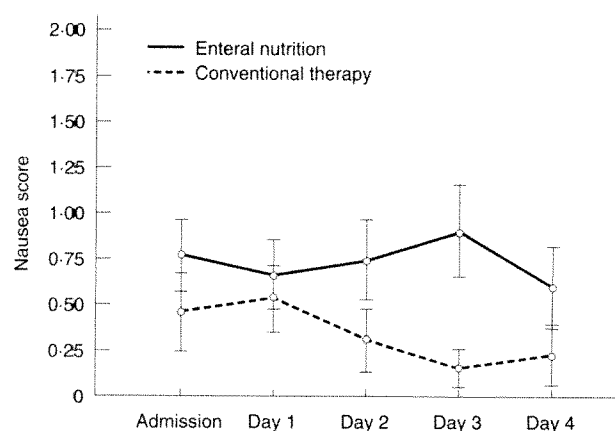


Fig. 3 Nausea scores in patients receiving early enteral nutrition or conventional therapy. Values are mean(s.e.m.)

Table 2 Intestinal permeability at admission and on day 4

		Intestinal permeability		χ^2	P
		Normal	Abnormal		
Admission					
Enteral	4	7	}	2.33	0.13
Conventional	1	10			
Day 4					
Enteral	0	8	}	4.94	0.03
Conventional	5	6			

Discussion

As studies in other critical illness states have demonstrated a reduction in infective complications in patients who receive enteral nutrition, it is rational to hypothesize that similar benefits may be obtained in patients with acute pancreatitis. However, valid concerns exist regarding the potential for adverse stimulation of the inflamed pancreas by the presence of nutrient in the upper gastrointestinal tract. Therefore this study has focused on the effect of early enteral nutrition on surrogate markers of the inflammatory response in patients with predicted severe acute pancreatitis.

In order to minimize any potential pancreatic stimulation, feed was delivered beyond the ligament of Treitz²⁵. No effect of early enteral nutrition on markers of the inflammatory response or on organ dysfunction was observed. These results differ from previously reported studies. Windsor *et al.*²⁶ reported a reduction in the systemic inflammatory response and surrogate markers of bacterial translocation in 34 patients with acute pancreatitis who received enteral nutrition compared with those who received parenteral nutrition. Similarly McClave *et al.*²⁷ reported a more rapid normalization of the physiological disturbance in 30 patients who received enteral nutrition compared with those who received parenteral nutrition. The differences between these studies and the present trial may arise for several reasons.

First, a median of 1.8 MJ/day was delivered, which constituted 21 per cent of daily calorific requirements. Although the original intention was to provide complete caloric requirements, a cautious step-up protocol was selected to minimize the risk of complications. This strategy appears to have been successful as reflected by the lack of difference in nausea scores and the absence of major feed-induced complications. However, Windsor *et al.*²⁶ delivered approximately 65 per cent of non-protein calories, while McClave *et al.*²⁷ provided 72 per cent of caloric requirements. Although the high rate of tube dislodgement may account for some of the discrepancy between the three studies, differences in disease severity may also be a factor. Patients in the studies reported by Windsor *et al.*²⁶ and McClave *et al.*²⁷ had lower serum CRP concentrations and prognostic scores than patients in the present study. It is likely that patients with mild acute pancreatitis have minimal intestinal ileus and therefore maximal rates of feeding can be achieved. In the present study, in which patients had more severe disease, feed volumes had to be limited because of intestinal ileus in almost a quarter of patients. Although Kalfarentzos *et al.*²⁸ demonstrated that 72 per cent of calorific requirements could be supplied through enteral nutrition in severe acute pancreatitis this

value was the mean over a period of 35 days. No value for the initial days following admission was provided. It is likely that intestinal ileus is maximal immediately after admission to hospital. Interestingly, although McClave *et al.*²⁷ provided 72 per cent of requirements during the total study period, only 30 per cent of requirements could be provided during the first 4 days.

It is not clear whether delivery of full caloric requirements by enteral nutrition is required to obtain benefit. It has been postulated that 'minimal enteral nutrition' limits the effects mediated by the intestinal tract in the systemic inflammatory response syndrome²⁹⁻³¹. The findings of the present study suggest that 'minimal enteral nutrition' does not modify the inflammatory response in acute pancreatitis. More interestingly, deterioration in intestinal function as measured by intestinal permeability in patients receiving enteral nutrition was observed. This observation is in contrast to evidence suggesting that luminal nutrition improves intestinal permeability⁹. The mechanisms responsible for this apparent deterioration of intestinal permeability are not clear. Bacterial colonization secondary to the feeding tubes may be a possible explanation but the increase in abnormal intestinal permeability in patients who received early enteral nutrition was not paralleled by altered IgG endotoxin antibody levels, suggesting no concomitant increase in bacterial translocation.

Another major difference between published studies is the use of parenteral nutrition. In the studies reported by Windsor *et al.*²⁶ and McClave *et al.*²⁷ patients in the no enteral nutrition group received parenteral nutritional support. Parenteral nutrition was therefore given to patients with mild disease who did not require routine nutritional supplementation. More significantly, Windsor *et al.*²⁶ maintained a nil-by-mouth regimen in the group that received parenteral nutrition until the seventh study day irrespective of the clinical condition, so a group of patients remained fasted despite clinical resolution of the disease. The delivery of parenteral nutrition to patients with mild disease and the abstinence until day 7 may account for the observed differences. Fong *et al.*³² have demonstrated that bowel rest and parenteral nutrition in normal volunteers is associated with an increased inflammatory response following a stimulus. Furthermore, malnourished patients have an impairment of intestinal function and increased serum markers of the acute-phase response³³. Therefore observed differences between patients who receive parenteral or enteral nutrition may not arise from a modulation of the disease process but may be a direct consequence of the treatment modality.

In summary, although enteral nutrition is feasible in patients with prognostically severe acute pancreatitis, it neither ameliorates nor exacerbates the inflammatory

response. With a growing body of experience that suggests clinical benefit, a large multicentre trial is required to evaluate this treatment modality before widespread introduction into everyday clinical practice.

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Preventive effect of preoperative portal vein ligation on endotoxin-induced hepatic failure in hepatectomized rats is associated with reduced tumour necrosis factor α production

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Background: Preoperative portal vein embolization successfully reduces the incidence of postoperative hepatic failure in which endotoxin is postulated to be involved. To identify the mechanism of this preventive effect, the relationship of endotoxin-induced liver injury with tumour necrosis factor (TNF) α and nitric oxide production in the peripheral blood, liver and spleen of rats subjected to preoperative portal vein branch ligation (PVL) was compared with that in rats undergoing sham operation.

Methods: Rats with PVL and those that underwent sham operation were subjected to resection of ligated liver lobes (PVL-Hx rats) and two-thirds hepatectomy (noPVL-Hx rats) respectively at day 5, followed by intravenous administration of endotoxin 200 μ g/kg body-weight at day 7. At various time intervals after endotoxin injection, the peripheral blood, liver and spleen tissues were harvested and analysed for TNF- α and nitric oxide production.

Results: The survival rates of noPVL-Hx and PVL-Hx rats at 48 h after endotoxin administration were 40 and 100 per cent respectively. The former rats showed more extensive liver injury as represented by higher serum aminotransferase and hyaluronate levels than the latter. Plasma concentrations of TNF- α at 1.5 h after endotoxin treatment were significantly higher in noPVL-Hx rats (mean(s.e.m.) 22 125(2175) pg/ml; $n=6$) than PVL-Hx rats (8344(4076) pg/ml; $n=6$) ($P<0.01$). Consistent with this, expression of TNF- α messenger RNA in the liver and spleen was suppressed in PVL-Hx rats. In two-thirds hepatectomized rats, plasma TNF- α concentrations after endotoxin administration at 1, 2 and 3 days (14 350(2186), 26 375(2478) and 23 000(3745) pg/ml respectively; $n=6$ each) were significantly higher than that before operation (9067(1559) pg/ml; $n=6$) ($P<0.05$), whereas those at 5 and 7 days (10 102(3616) and 8580(1427) pg/ml respectively; $n=6$ each) showed no significant increase. Furthermore, nitric oxide production in peripheral blood and liver was suppressed by preoperative PVL.

Conclusion: Prevention of endotoxin-induced liver failure by preoperative PVL is associated with reduced production of TNF- α in the later phase of liver regeneration.

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Introduction

Hepatic failure is an occasional complication after extensive liver resection for hepatocellular carcinoma (HCC) and has a high mortality rate^{1,2}. To minimize postoperative liver dysfunction, percutaneous transhepatic portal vein embolization (PTPE) has been developed^{3–7}, whereby an embolized part bearing the tumour mass becomes atrophic, whereas a non-embolized part, i.e. the future remnant liver, undergoes compensatory hypertrophy before operation. This procedure can be performed without causing major complications and improves the prognosis of patients with

HCC after liver resection even in the presence of severe liver cirrhosis^{8,9}. Experimental studies have been done using a rat model with portal vein embolization¹⁰ and portal vein branch ligation (PVL)^{11–13}, but the mechanism of the favourable therapeutic effect has not been fully elucidated.

It is assumed that endotoxin may be involved in the pathogenesis of postoperative hepatic failure from clinical and experimental observations that bacterial translocation to the liver or endotoxaemia often takes place in the early time period after major hepatectomy^{14,15} and thus the induced hepatic inflammation promotes hepatic failure¹⁶. Low-dose endotoxin that causes little harm to untreated

rats acutely causes severe liver injury with a high mortality rate in hepatectomized rats when administered 2 days after operation¹⁷. The pathophysiological features of this rat model, i.e. massive hepatic necrosis and ascites formation, are very similar to those of human postoperative hepatic failure¹⁷. Macrophage activation is considered to be responsible for the liver injury in this model^{18,19}. It has recently been found that tumour necrosis factor (TNF) α released from endotoxin-activated hepatic macrophages induces morphological and functional alterations to sinusoidal endothelial cells, which leads to microcirculatory disturbance and ultimately to hepatic necrosis²⁰, suggesting the involvement of this cytokine in the development of postoperative hepatic failure.

In this study, to demonstrate the preventive effect of PVL on postoperative hepatic failure from the aspect of TNF- α , TNF- α production in peripheral blood and the extent of its messenger RNA (mRNA) expression in liver and spleen after endotoxin administration were compared in hepatectomized rats with and without preoperative PVL. The production of nitric oxide, which is similarly released from endotoxin-activated Kupffer cells^{21,22}, was also studied.

Materials and methods

Animals

One hundred and ninety-six male Sprague-Dawley rats (200–250 g body-weight) were purchased from Clea Japan (Tokyo, Japan). They were housed under specific pathogen-free conditions with a 12-h light-dark cycle at a constant temperature of 24°C, and fed standard chow pellets and water *ad libitum*. They were allowed to acclimatize to laboratory conditions for 4–6 days before use. Experiments were performed in accordance with the standard guideline for animal experiments of Kagawa Medical University.

Portal vein branch ligation and partial hepatectomy

Under general anaesthesia with isoflurane (Abbott Laboratories, North Chicago, Illinois, USA), 70 rats were subjected to ligation of the left portal vein branch, which supplied the left and middle lobes, corresponding to approximately two-thirds of the whole liver volume. Five days later, when ligated liver lobes had almost complete hypertrophic changes²³, they were resected (PVL-Hx rats). Eighty animals were subjected to sham operation on day 0 and subsequent two-thirds partial hepatectomy on day 5 according to Higgins and Anderson²⁴ (noPVL-Hx rats). Thirty-six of the remaining rats were subjected to two-thirds partial hepatectomy alone and ten to PVL alone.

Endotoxin administration

Forty-eight hours after hepatectomy, endotoxin (*Escherichia coli* 0127 : B8; Difco Laboratories, Detroit, Michigan, USA) 200 μ g/kg body-weight dissolved in saline at a concentration of 250 μ g/ml was injected via the tail vein. This time interval has been demonstrated to cause the most serious liver failure in hepatectomized rats¹⁷.

Survival rates

Ten PVL-Hx rats, 20 noPVL-Hx rats and ten rats with PVL alone were used. Survival rates were measured at 48 h after endotoxin administration for the former two and PVL for the latter.

Biochemical analyses of peripheral blood

Thirty PVL-Hx rats and 30 noPVL-Hx rats were used for the time course analysis. Six rats each per group were killed at 48 h before (immediately before hepatectomy) and 0, 1.5, 3 and 5 h after endotoxin injection. Thirty-six rats that received two-thirds hepatectomy alone were also used for the time course analysis immediately before and 1, 2, 3, 5 and 7 days after hepatectomy. Six rats were used at each time point. The abdomen was opened under general anaesthesia with isoflurane. Heparinized and non-heparinized peripheral blood was taken from the inferior vena cava. Serum and plasma were stored at –80°C before use. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and total bilirubin (TBil) were determined by a Hitachi 7050 automatic analyser (Hitachi, Tokyo, Japan). Serum hyaluronate levels, an index of hepatic sinusoidal endothelial function^{25,26}, were measured with a sandwich binding protein assay system (Chugai Pharmaceutical, Tokyo, Japan)²⁷. The plasma TNF- α level was measured in a 96-well microtitre plate by using a TNF- α test kit (Genzyme, Cambridge, Massachusetts, USA) based on an enzyme-linked immunosorbent assay. All samples were tested in duplicate. The plate was read on a microplate reader (MTP-120; Corona Electric, Ibaragi, Japan) at 450 nm. The concentration of TNF- α was calculated from a standard curve.

Histology

After collecting peripheral blood, the liver was perfused with saline via the portal vein. A part of the liver and spleen were resected and used for Northern blot analysis. A fixative containing 1.5 per cent glutaraldehyde in cacodylate buffer 0.062 mol/l, pH 7.4, plus 1 per cent sucrose was subsequently infused. Specimens were obtained from several

different portions of the caudate process and right lobe, and cut into small pieces. They were postfixed in 1 per cent osmium tetroxide in phosphate buffer 0.1 mol/l, pH 7.4, for 2 h, dehydrated in an ethanol series and embedded in polybed (Polyscience, Warrington, Pennsylvania, USA). Sections of 0.5 µm in thickness were cut, stained with toluidine blue and observed by light microscopy.

Counting of Kupffer cells

Using toluidine blue-stained sections, the number of Kupffer cells in ten randomly chosen microscopic fields at a magnification of $\times 400$ (0.84 mm²) was counted as described previously²⁸. Three or four livers were analysed for each experimental group, and the average density of cells was calculated.

Northern blot analysis

The liver and spleen samples resected after saline perfusion were homogenized with a Polytron homogenizer (Kinematica, Littau/Lucerne, Switzerland). Total RNA was extracted from small portions of homogenized liver and spleen (100 mg tissue), using guanidinium-phenol-chloroform²⁹. Each 20 µg of extracted RNA was denatured and subjected to electrophoresis in 1 per cent agarose gel containing 7.4 per cent formaldehyde for 3 h at 100 V. Electrophoresed RNA was transferred to a nylon membrane (Hybound-N; Amersham, Bucks, UK). After fixation, the membrane was incubated for 2 h at 42°C in a prehybridization buffer containing $5 \times$ saline sodium citrate (SSC; sodium chloride 3 mol/l and sodium citrate 0.3 mol/l), $5 \times$ Denhardt's solution, 50 per cent formamide, 0.5 per cent sodium dodecyl sulphate (SDS) and salmon sperm DNA 20 µg/ml. The membrane was then incubated in the same buffer supplemented with complementary DNA for rat TNF- α ^{30,31}, which was labelled with [³²P]2'-deoxycytidine 5'-triphosphate using a multiprime labelling system (Amersham). After overnight incubation at 42°C, the membrane was washed twice with $2 \times$ SSC containing 0.1 per cent SDS and then with $0.1 \times$ SSC containing 0.1 per cent SDS. Autoradiography was performed using a Fuji BAS 2000 Bio-imaging analyser (Fuji-Photo-Film, Tokyo, Japan). Quantification of bands was done by using the NIH Image software (NIH, Bethesda, MD, USA).

Electron paramagnetic resonance spectroscopy of nitrosyl complexes

Another 30 PVL-Hx and 30 noPVL-Hx rats were used for the time course analysis of nitric oxide production. Liver samples excised without saline perfusion were homoge-

nized. Electron paramagnetic resonance (EPR) spectroscopy was used to detect haemoglobin nitrosyl complexes (HbNO)^{32,33}, a marker for nitric oxide generation, according to previous papers³⁴⁻³⁶. Heparinized whole blood and liver homogenates were immediately transferred to EPR quartz tubes and frozen in liquid nitrogen. EPR spectra were obtained with a JES-RE1X spectrometer (JEOL, Tokyo, Japan) at 9.26 GHz using a finger-tip liquid nitrogen Dewar flask. A typical setting for spectrometers was 3270 Gauss of magnetic field, 5 mW of incident microwave power, 500 Gauss of sweep width and 120 s of scan time. The EPR signal from chromium (III) (Cr³⁺) in magnesium oxide (MgO) was used as the *g*-value marker. The data were transferred to a computer, where baseline correction and double integration were performed.

Statistical analysis

Data were expressed as mean(s.e.m.). Unpaired Student's *t* test was used for statistical analysis.

Results

Organ : body weight ratio of the remnant liver and spleen

In PVL-Hx rats, non-ligated liver lobes or a future remnant liver showed an increase in organ : body weight ratio after PVL as the result of compensatory hypertrophy for atrophy of the ligated lobes. After the resection of ligated lobes at day 5, the ratio continued to increase (*Fig. 1a*). In noPVL-Hx rats, the remaining liver lobes rapidly increased this ratio from day 5, reaching approximately 75 per cent of that in PVL-Hx rats (*Fig. 1a*).

The spleen : body weight ratio in PVL-Hx rats increased to day 5 after PVL possibly owing to an increase in portal pressure, and further increased after resection of the ligated liver lobes (*Fig. 1b*), while that of noPVL-Hx rats underwent a rapid increase after partial hepatectomy at day 5, reaching a similar value to that of PVL-Hx rats at day 7 (*Fig. 1b*).

Effect of portal vein ligation on endotoxin-induced hepatic injury and survival rate

All ten PVL-Hx rats survived after administration of low-dose endotoxin (200 µg/kg body-weight) 48 h after hepatectomy, whereas 12 of 20 noPVL-Hx rats died within 48 h, mostly between 8 and 10 h, after injection. All rats that died showed a prominent feature of bloody ascites, bilirubinuria and histologically massive hepatic necrosis.

In noPVL-Hx rats, serum levels of ALT (*Fig. 2a*), TBil (*Fig. 2b*) and hyaluronate (*Fig. 2c*) increased considerably at

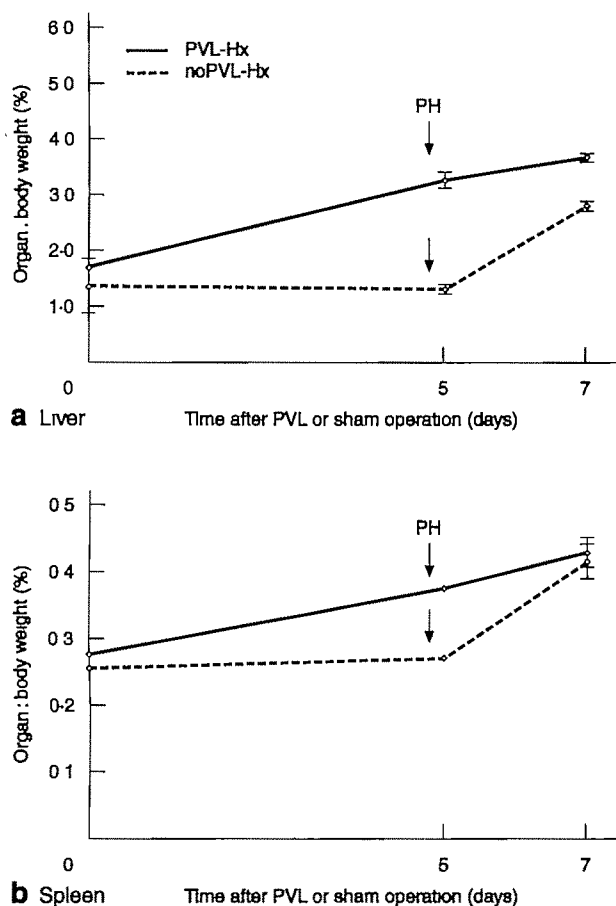


Fig. 1 Time course of the ratio of the weight of the remnant liver (a) and spleen (b) to body-weight in noPVL-Hx rats and PVL-Hx rats after sham operation and portal vein ligation (PVL) respectively. Partial hepatectomy (PH) was performed at day 5 as indicated by arrows. Values are mean(s.e.m.) ($n = 6$ per time point)

later than 3 h, although the values of ALT and hyaluronate were already high at the time of endotoxin injection, probably as a result of the two-thirds hepatectomy. Histological analysis demonstrated that massive hepatic necrosis developed at later than 5 h (data not shown) as reported previously²⁰. In PVL-Hx rats, on the other hand, serum levels of ALT, TBil and hyaluronate showed only a slight increase; values were significantly lower than those in noPVL-Hx rats, and histological changes were negligible.

Effect of portal vein ligation on tumour necrosis factor α expression

Plasma TNF- α was not detected in hepatectomized rats at 48 h after operation (data not shown), consistent with previous reports^{19,20,37}. After endotoxin administration, the plasma TNF- α concentration increased dramatically at

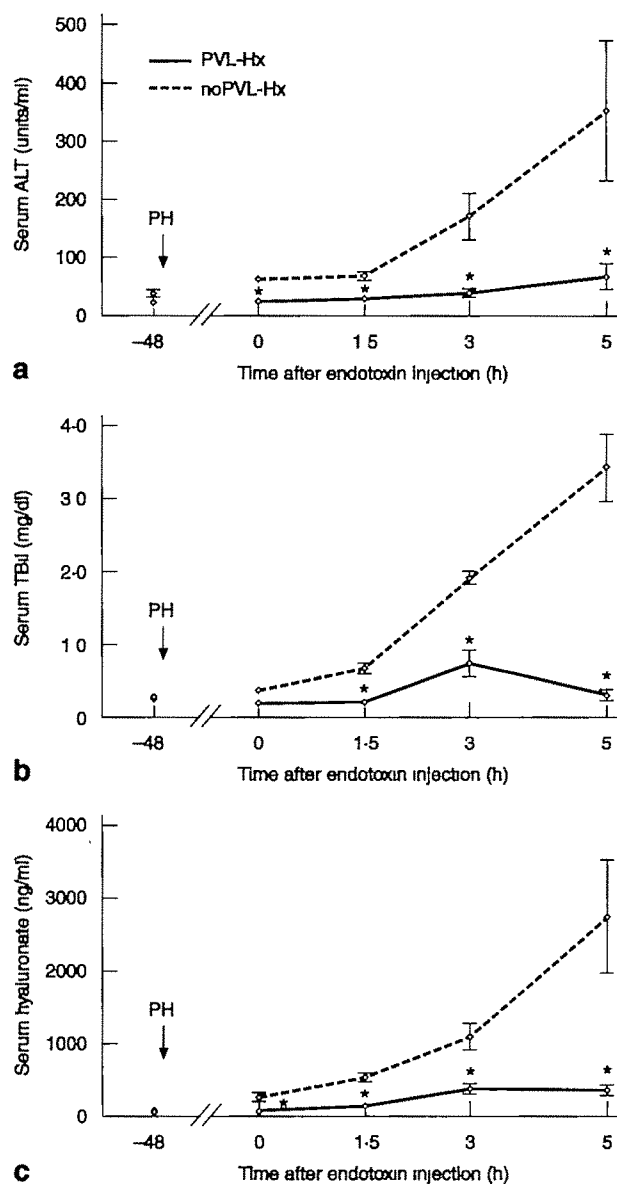


Fig. 2 Time course of serum levels of a alanine aminotransferase (ALT), b total bilirubin (TBil) and c hyaluronate after intravenous injection of endotoxin 200 $\mu\text{g/kg}$ body-weight in noPVL-Hx and PVL-Hx rats. Partial hepatectomy (PH) was performed 48 h before endotoxin injection. Values are mean(s.e.m.) ($n = 6$ per time point). * $P < 0.01$ versus noPVL-Hx rats (unpaired Student's t test)

1.5 h and then declined by 3 h in noPVL-Hx rats (Fig. 3). In PVL-Hx rats it was significantly lower at 1.5 h (Fig. 3). In accordance with these data, TNF- α mRNA expression in the liver and spleen from PVL-Hx rats was less than that in noPVL-Hx rats at 1.5 h (Fig. 4).

These differences in TNF- α production in response to endotoxin between PVL-Hx and noPVL-Hx rats might

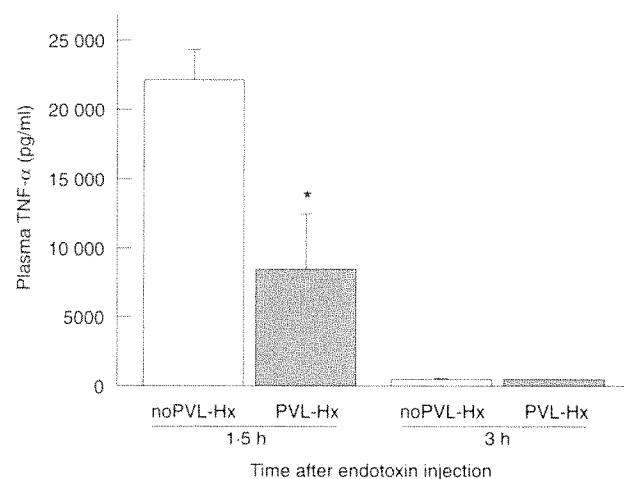


Fig. 3 Plasma tumour necrosis factor (TNF) α concentrations at 1.5 and 3 h after endotoxin administration in noPVL-Hx and PVL-Hx rats. Partial hepatectomy was performed 48 h before endotoxin injection. Values are mean(s.e.m.) ($n = 6$ per time point). * $P < 0.01$ versus noPVL-Hx rats (unpaired Student's t test)

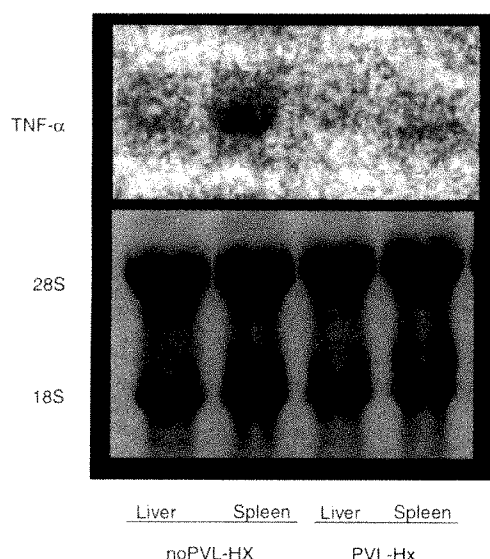


Fig. 4 Northern blot analysis of tumour necrosis factor (TNF) α expression in the liver and spleen of noPVL-Hx rats and PVL-Hx rats at 1.5 h after endotoxin administration. Partial hepatectomy was performed 48 h before endotoxin injection

derive from differences in the stage of liver regeneration or time intervals after the onset of regeneration, i.e. 2 days in noPVL-Hx rats and 7 days in PVL-Hx rats. A time course analysis of plasma TNF- α levels during liver regeneration was therefore conducted. Plasma TNF- α levels at 1.5 h after endotoxin injection were much higher during the first

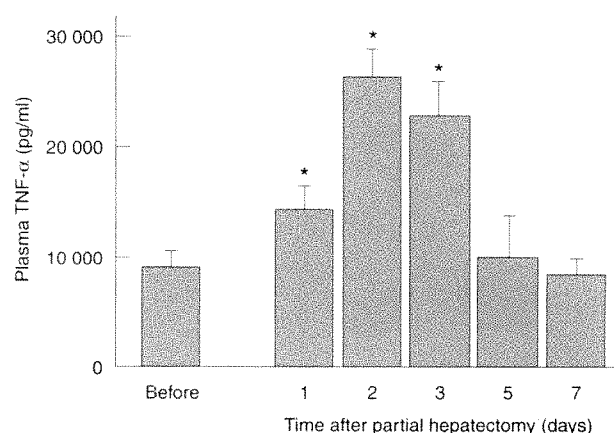


Fig. 5 Plasma tumour necrosis factor (TNF) α concentrations in hepatectomized rats before and 1–7 days after operation, measured at 1.5 h after intravenous injection of endotoxin 200 μ g/kg body-weight. Values are mean(s.e.m.) ($n = 6$ per time point). * $P < 0.05$ versus before partial hepatectomy (unpaired Student's t test)

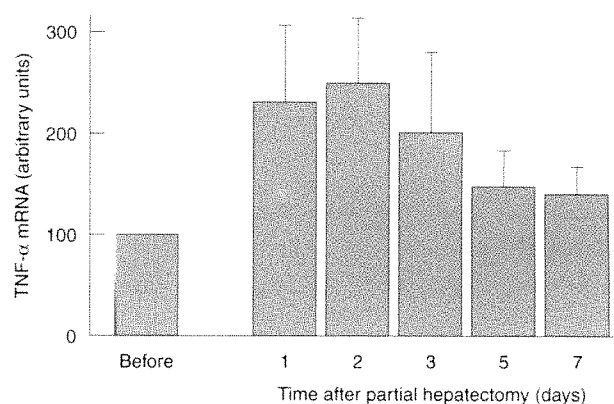


Fig. 6 Densitometric quantitation of Northern blot band of tumour necrosis factor (TNF) α from the liver of hepatectomized rats before and 1–7 days after partial hepatectomy, analysed at 1.5 h after intravenous injection of endotoxin 200 μ g/kg body-weight. Values are expressed as means(s.e.m.). Three different experiments were performed. mRNA, messenger RNA

3 days compared with 5 and 7 days after partial hepatectomy (Fig. 5). Consistent with this result, TNF- α mRNA expression in the liver at 1.5 h was higher in the first 3 days compared with 5 and 7 days after partial hepatectomy (Fig. 6).

Nitric oxide production in peripheral blood and liver

In whole blood, the EPR signals of three-line hyperfine structure indicative of HbNO were not detectable at 0 and

1.5 h after endotoxin injection both in noPVL-Hx and PVL-Hx rats, and became evident at 3 and 5 h. Total HbNO concentration obtained from the total integrated area of HbNO in the EPR spectra was significantly lowered by PVL at 5 h. In the liver, although HbNO signals overlapped with an unknown signal of free radicals at g approximately 2.0, as reported previously^{36,38}, HbNO signals could be detected at later than 3 h both in noPVL-Hx and PVL-Hx rats. The integrated areas of total HbNO obtained by subtraction of overlapped signals were significantly lower in PVL-Hx rats than noPVL-Hx rats at 3 and 5 h.

Kupffer cells

The number of Kupffer cells per unit area (0.84 mm^2) of liver parenchyma was $87.3(5.9)$ ($n=3$) before hepatectomy. Both noPVL-Hx rats and PVL-Hx rats showed an increased number of Kupffer cells immediately at day 7 after sham operation and PVL respectively, but the latter rats exhibited a larger number ($213.3(5.2)$; $n=3$) than the former ones ($154.3(1.5)$; $n=4$). Taking liver weight into account, the total number of Kupffer cells in the liver of PVL-Hx rats was estimated to be approximately twice that of noPVL-Hx rats.

Discussion

Major hepatectomy causes hypoalbuminaemia, cholestasis and coagulopathy before complete regeneration of remnant liver lobes, often leading to sepsis, haemorrhage and leakage from the bilioenteric anastomosis³⁹. For the purpose of minimizing these postoperative complications, PTPE as a modification of PVL has been employed clinically to induce preoperative hypertrophy of the remnant liver³⁻⁷. The benefit of this procedure in terms of reducing liver failure has been explained by a net gain of functional hepatocytes through rapid induction of hepatocyte proliferation after hepatectomy⁶ and increased capacity for hepatocytes to retain hepatic energy charge^{11,12}. In this study, a rat model of endotoxin-induced hepatic failure was used and it was demonstrated that PVL prevented the postoperative hepatic failure. The weight of remnant liver lobes of PVL-Hx rats exceeded that of noPVL-Hx rats by approximately 30 per cent on endotoxin administration, which raises the possibility that the lower mortality rate in the former rats may be due to the relatively low dose of endotoxin. However, this is not likely because PVL-Hx rats treated with twice the dose, i.e. endotoxin $400 \mu\text{g/kg}$ body-weight, did not die after hepatic failure (Yachida S, unpublished observation).

In this study, TNF- α was not detectable in the serum 48 h after partial hepatectomy, consistent with previous

reports^{19,20,37}. However, this does not imply that the cytokine is not released from activated macrophages in response to gut-derived endotoxin after partial hepatectomy, because there is evidence that TNF- α is produced locally in the earlier phase after partial hepatectomy⁴⁰, especially in patients with cirrhosis, in whom major liver resection and portal hypertension predispose to bacterial translocation and endotoxaemia^{14,41,42}.

Since microcirculatory disturbance caused by macrophage-derived TNF- α has been proposed as a major cause of massive hepatic necrosis or hepatic failure after hepatectomy^{19,20}, the mechanism of the preventive effect of PVL on postoperative hepatic failure was investigated in relation to TNF- α production. Prevention by PVL was associated with lower plasma TNF- α levels, and hepatic and splenic TNF- α mRNA expression 1.5 h after endotoxin administration. Such reduced responsiveness in PVL-Hx rats is considered to be related to the phase of liver regeneration with respect to endotoxin administration, i.e. 7 days after the onset *versus* 2 days in noPVL-Hx rats, because animals showed higher plasma TNF- α levels and hepatic TNF- α mRNA expression at 1-3 days after partial hepatectomy than at 5-7 days. (Although these data were from the remnant liver after two-thirds hepatectomy, similar events are expected to occur in non-ligated lobes after PVL as deduced from previous findings that Kupffer cells similarly increased in density²³ as in two-thirds hepatectomized liver²⁸ and endotoxin-induced liver injury occurred more frequently (four of seven) than in sham-operated rats (one of six), probably as the result of an increased Kupffer cell response¹⁰.) Expansion of the Kupffer cell population during liver regeneration after PVL is considered to result predominantly from local proliferation⁴³ and additionally from recruitment from circulating monocytes⁴⁴.

The present finding that the number of Kupffer cells on endotoxin administration was larger in PVL-Hx rats than noPVL-Hx rats indicates that the decreased production of TNF- α in PVL-Hx rats did not result from a decreased number of Kupffer cells but probably from a lowered activity of individual Kupffer cells. It has been reported that Kupffer cells are activated in the early phase (1-3 days) after hepatectomy as far as TNF- α production *in vitro*⁴⁵, phagocytic activity⁴⁶ and superoxide anion production¹⁷ are concerned, being 'primed' secondary to an increased gut-derived endotoxin load¹⁸. Inhibition of Kupffer cell function is beneficial for the prevention of endotoxin-induced liver injury after partial hepatectomy¹⁹. Although Kupffer cell activation may also be induced by hepatectomy performed 5 days after PVL, the extent is assumed to be much lower from the smaller increase (13 per cent as calculated from the data in Fig. 1a) in remnant liver: body

weight ratio after resection of ligated lobes compared with that induced after two-thirds hepatectomy (119 per cent). It is thus conceived that the therapeutic advantage of PVL can be obtained by shifting the time point of a hepatectomy-associated endotoxin load to a later phase (7 days) of liver regeneration, in which Kupffer cell activation declines.

The spleen is another major site of endotoxin clearance and generation of macrophage-derived cytokines as its consequence^{47,48}. When hepatectomized, it shows a compensatory increase in the uptake of endotoxin to 190 per cent at maximum⁴⁶. The increased splenic TNF- α mRNA expression observed here after hepatectomy must be related to this phenomenon. The spleen may contribute to the endotoxin-induced liver injury after partial hepatectomy because splenectomy attenuates this disorder¹⁹. The lower splenic TNF- α mRNA expression in PVL-Hx rats compared with noPVL-Hx rats may be also related to the prevention of hepatic failure.

Hepatocytes and Kupffer cells stimulated with endotoxin generate large amounts of nitric oxide^{21,22,49,50}. In this study, PVL-Hx rats produced a smaller amount of hepatic nitric oxide than noPVL-Hx rats, consistent with the present interpretation that Kupffer cells are less activated in PVL-Hx rats. The role of nitric oxide in the development of liver injury is controversial⁵¹; some studies indicate its cytotoxic action on hepatocytes through suppression of protein synthesis⁴⁹ and inhibition of mitochondrial electron transport⁵², while others report its protective function against cell damage via neutralization of superoxide radicals⁵³ and inhibition of microcirculatory dysfunction^{54,55}. Whether nitric oxide generated in this model acted as a direct cause of hepatotoxicity or merely as the result of a feedback mechanism of liver injury requires further study.

In conclusion, the favourable effect of preoperative PVL is closely associated with lowered TNF- α production.

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Localization of matrix metalloproteinase 2 within the aneurysmal and normal aortic wall

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Background: Current research has shed new light on the role of matrix metalloproteinase (MMP) 2 in the development of abdominal aortic aneurysms (AAAs). MMP-2 is a major protease in the wall of small aneurysms and is produced at increased levels by smooth muscle cells derived from AAAs compared with normal controls. *In vivo*, MMP-2 is produced as an inactive proenzyme that is activated predominantly by the cell membrane-bound enzyme, membrane type 1 matrix metalloproteinase (MT1-MMP). This study investigated the production of the MMP-2-MT1-MMP-tissue inhibitor of metalloproteinases (TIMP) 2 system within the wall of aortic aneurysms and in age-matched control arterial tissue.

Methods: Arterial tissue from four patients with aortic aneurysms and four age-matched aortic samples was examined for the production and expression of MMP-2, TIMP-2 and MT1-MMP protein using immunohistochemistry, *in situ* hybridization and *in situ* zymography.

Results: All components of the MMP-2-TIMP-2-MT1-MMP enzyme system were detected in the arterial wall of both aneurysm and control samples, specifically in the medial tissue. The enzymes co-localized with medial smooth muscle cells. Gelatinolytic activity was localized to elastin fibres in normal and aneurysmal aorta.

Conclusion: The presence of MT1-MMP within the media of arterial tissue suggests a powerful pathway for the activation of MMP-2. The localization of the MMP-2-TIMP-2-MT1-MMP enzyme system to the medial layer of the arterial wall gives support to the concept that this system may play an aetiological role in the pathogenesis of AAAs.

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Introduction

Abdominal aortic aneurysms (AAAs) are characterized by dramatic localized remodelling of the extracellular matrix (ECM)¹⁻⁷, the presence of a chronic inflammatory infiltrate⁸ and an associated increase in the production of activated matrix metalloproteinases (MMPs)⁹. These events are manifest as a weakening of the aortic media, due to destruction of elastin fibres¹⁰⁻¹² and smooth muscle cells (SMCs)¹³. Loss of structural integrity within the aortic media may lead to inability of the vessel wall to resist the dilating force of the arterial circulation, with the subsequent development of an aneurysm¹⁴.

Abdominal aneurysms have historically been associated with increased levels of systemic and local proteolysis. Raised levels of systemic neutrophil elastase have been demonstrated in patients with an AAA, both before and after

operation¹⁵⁻¹⁷, and increased MMP production within the aneurysm wall has also been reported consistently. MMP-1 (interstitial collagenase), MMP-3 (stromelysin 1) and MMP-9 (gelatinase B) are the most commonly identified proteases amongst those thought to have involvement in aneurysm development and progression¹⁸⁻²⁰.

The majority of studies investigating the pathogenesis of abdominal aneurysms have analysed biopsies of the aneurysm wall, which represents the end-stage of a pathological process. With this form of experimental design it is difficult to separate primary aetiological factors from secondary degenerative effects. However, recent studies using cell culture techniques to define the role of individual cell types have suggested that the mesenchyme-derived MMP-2 may be the dominant protease in the initiation of aneurysm development^{21,22}, and reports of the biochemical composition of small aneurysms support these observations²³.

The apparent increase in production of MMP-2 in early aneurysms may potentially be significant in initiating degradation of elastin tissue within the aortic media²⁴. However, mesenchymal cells secrete MMP-2 as an inactive precursor, which must be processed to an active form for elastolysis to occur²⁵. *In vivo*, the principal activator of MMP-2 is the membrane type 1 matrix metalloproteinase (MT1-MMP). This is a relatively recently characterized member of the MMP family²⁶, which contains a trans-membrane domain within its structure^{27–29}. MT1-MMP binds the inactive pro-MMP-2–tissue inhibitor of metalloproteinases (TIMP) 2 complex at the cell surface and cleaves the pro-domain from MMP-2, thereby activating the enzyme and localizing the collagenase activity at the cell membrane³⁰. The importance of MT1-MMP as a potent activator of MMP-2 is supported by a number of studies demonstrating a close association between MT1-MMP expression and tumour invasion and metastasis^{31–34}.

The role of TIMP-2 in this system is complex. TIMP-2 is the physiological inhibitor of MMP-2. However, binding of pro-MMP-2 by MT1-MMP is TIMP dependent³⁵, although *in vitro* systems indicate that TIMP-2 is inhibitory at higher concentrations³⁶. Thus, a complex and dynamic relationship exists between MMP-2, MT1-MMP and TIMP-2 that may control the degradation of elastin within the arterial wall.

This study investigated the production and location of the MMP-2–MT1-MMP–TIMP-2 enzyme system within normal and aneurysm aortic wall.

Patients and methods

Collection and preparation of aortic samples

The histological studies described in this study were performed using aneurysm tissue obtained during elective surgical repair from the aortic wall 2 cm distal to the left renal vein, to standardize the collection point. Tissue was obtained from four men aged 67, 67, 69 and 73 years with an AAA of diameter 7.0, 7.5, 6.5 and 8.0 cm respectively. Control tissue was obtained from the same site from age-matched cadavers who had died from causes unrelated to aneurysm disease and had no evidence of macroscopic peripheral vascular disease (all aortas less than 2.5 cm in diameter). All control samples were obtained within 24 h of death. Samples were divided into two pieces. One half was frozen on to cork blocks in liquid nitrogen. The remainder were fixed in 4 per cent paraformaldehyde for 6 h, processed and embedded in paraffin wax.

The median ages of controls and patients with AAA were not significantly different (control 64.5 (58.0–69.5) years

versus AAA 68.0 (64.5–73.5) years; $P=0.057$, Mann–Whitney U test).

Immunohistochemical staining of tissue sections

A three-step, indirect staining protocol was used. Primary murine monoclonal antibodies were purchased from Chemicon, Harrow, UK (MMP-2, MT1-MMP, TIMP-2); Sigma, Poole, UK (smooth muscle α -actin) and Dako, Ely, UK (macrophage (CD68) and biotinylated antimouse secondary antibody). Vectastain preformed avidin–biotin–horseradish peroxidase conjugated complex (ABC) was purchased from Vector Laboratories, Burlingame, California, USA. Diaminobenzidine (DAB) peroxidase substrate was purchased from Merck, Lutterworth, UK. The antibody to MMP-2 detected both active and latent enzyme, while the antibody to MT1-MMP recognized latent, active and cleaved enzyme.

Paraffin wax-embedded sections (5 μ m) were applied to silane-coated glass microscope slides and allowed to dry overnight at 37°C. The sections were dewaxed and hydrated by sequential submersion in xylene, 99 per cent ethanol, 95 per cent ethanol and water (for 1 min each), then any intrinsic peroxidase activity was blocked by submersion in 6 per cent hydrogen peroxide for 10 min. The slides were washed in phosphate-buffered saline (PBS) for 5 min and blotted carefully. Normal goat serum (diluted 1 in 20; Dako) was applied to the slides to cover the sections and left for 10 min in a humid chamber to reduce non-specific antibody binding. The slides were drained and the sections carefully wiped. A 100- μ l aliquot of primary antibody (diluted appropriately in 5 per cent goat serum) was added to the sections and the slides were returned to the humid chamber where they were left for 18 h at 4°C. Unbound antibody was removed by two 10-min washes in PBS.

The slides were wiped and returned to the humid chamber where 100 μ l secondary antibody (diluted 1 in 600 in PBS) was applied to the sections, which were incubated for 30 min at room temperature. Unbound secondary antibody was removed by two 10-min washes in PBS. The slides were again wiped and returned to the humid chamber, where 100 μ l preformed ABC complex was applied to the sections, and incubated at room temperature for 30 min. Excess ABC complex was removed by two 10-min washes in PBS.

DAB substrate (0.05 per cent) was filtered on to the slides, which were left at room temperature for 5 min. The slides were washed briefly in copper sulphate solution 25 mmol/l, then in running water. Cellular nuclei were stained by immersion of the slides in haematoxylin for 30 s and washing until clear in running water. The sections were then dehydrated and cleared by sequential immersion in 95

per cent ethanol, 99 per cent ethanol and xylene (1 min each). They were then mounted under glass coverslips using XAM mountant (Merck, Lutterworth, UK). Regions of immunological reactivity were visualized by a dark brown stain, produced where the DAB was oxidized by horseradish peroxidase (HRP) to produce a red-brown precipitate.

In situ hybridization

MMP and TIMP probes were designed according to sequence data from the Genbank database. All probes were a cocktail of oligonucleotides, each of 20 to 30 bases in length, as described in Table 1. Antidigoxin secondary antibody was purchased from Sigma.

Probe labelling

To visualize the probes, they were end-labelled with digoxin. This was achieved using a DNA oligonucleotide tailing kit (Boehringer Mannheim, Lewes, UK) according to the manufacturer's protocol. Digoxin-conjugated 2'-deoxyuridine 5'-triphosphate (dUTP) and unconjugated 2'-deoxyadenosine 5'-triphosphate (dATP) nucleotides were added, typically around 20 bases to each probe molecule. A labelling reaction was made up as follows: 4 µl 5× tailing buffer (potassium cacodylate 1 mol/l, Tris-hydrochloric acid 125 mmol/l, bovine serum albumin (BSA) 1.25 mg/ml), cobalt chloride 5 mmol/l, digoxin-conjugated dUTP 50 mmol/l, dATP 500 nmol/l, 1 µg oligonucleotide and 50 units Tdt enzyme; the reaction was made up to 20 µl with DEPC water and allowed to proceed at 37°C for 1 h. Following the labelling reaction the probes were purified to remove reaction components and unincorporated nucleotides by passing through a QiaQuick oligonucleotide purification spin-column (Qiagen, Crawley, UK). The collected probe solution was stored at -20°C for future use.

Table 1 *In situ* hybridization probe oligonucleotide sequences

Target	Oligonucleotide sequence	Position
MMP-2	CCT CAT TGT ATC TCC AGA ATT TGT CTC CAG	1704-1733
	ACC GGT CCT TGA AGA AGA TCT CAC CAC	1398-1427
	CTC CAG AAT TTG TCT CCA GC	1703-1722
MT1-	CCC CTT GTA GAA GTA AGT GAA GAC TTC ATC	1590-1619
MMP	CCT CAT CAA ACA CCC AAT GCT TGT CTC CTT	1327-1356
	CAT CCA GAA GAG AGC AGC ATC AAT CTT GTC	1414-1443
	AAT TTG CCA TCC TTC CTC TCG TAG GCA GTG	1286-1315
TIMP-2	ATA TTC CTT CTT TCC TCC AAC GTC CAG CGA	571-600
	AAC TCT ATA TCC TTC TCA GGC CCT TTG AAC	504-533
	GTT CTT CTC TGT GAC CCA GTC CAT CCA GAG	787-816
	GTA CCT GTG GTT CAG GCT CTT CTT CTG GGT	685-714

MT1-MMP, membrane type 1 matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases

Probe hybridization

Tissue specimens were fixed in 4 per cent paraformaldehyde for 24 h, then embedded in paraffin wax. Sections were cut to 6 µm on a microtome and applied to silane-coated slides, where they were allowed to dry at 37°C for 24 h. Tissue architecture was assessed by staining selected slides in haematoxylin and eosin to visualize cell nuclei and ECM.

Sections were dewaxed and hydrated as above. Slides were immersed in a solution of 2× SSC (sodium hydroxide 300 mmol/l, trisodium citrate 30 mmol/l) for 10 min at 70°C, then washed in diethyl pyrocarbonate (DEPC) water for 5 min. Slides were drained, 100 µl proteinase K (2 or 5 µl/ml of a 1-mg/ml stock solution) was added to each section, and they were incubated in a humid chamber at 37°C for 60 min.

The slides were washed with cold DEPC water for 5 min, with cold 0.4 per cent paraformaldehyde for 20 min, rinsed in DEPC water for 5 min, and then 50 µl prehybridization solution (sodium chloride 600 mmol/l, Tris-hydrochloric acid 50 mmol/l, pH 7.5, 0.1 per cent sodium pyrophosphate, 0.2 per cent polyvinyl pyrrolidone, 0.2 per cent ficoll, ethylenediamine tetra-acetic acid (EDTA) 5 mmol/l, 10 per cent dextran sulphate, 30 per cent formamide, heat-denatured salmon sperm DNA 150 ng/ml) was added to each slide. Slides were incubated for 1 h at 37°C in a humid chamber. The probe was mixed with 50 µl prehybridization solution at a concentration of 500 ng/ml and added directly to the sections, over which coverslips were placed. Access and annealing of the probe was allowed to take place overnight at 37°C in a humid chamber.

Coverslips were removed and the slides washed twice in wash buffer (2× SSC, 30 per cent formamide) for 10 min at 37°C. Slides were submerged in blocking solution (3 per cent BSA, 0.1 per cent triton X-100 in TBS) for 10 min, and alkaline phosphatase-conjugated antidigoxin antibody was added directly to this at a dilution of 1 in 600. This was allowed to bind for 30 min at room temperature. Unbound antibody was removed by two 5-min washes in PBS. Bound probe was visualized by the addition of 200 µl nitroblue-tetrazolium/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP) solution (NBT 0.6 mg/ml, BCIP 0.4 mg/ml, levamisole 1 mmol/l, Tris-hydrochloric acid 100 mmol/l, pH 9.5, magnesium chloride 50 mmol/l, sodium chloride 100 mmol/l; made up in DEPC water) to each section, coverslips were added and the slides were incubated in dark conditions at room temperature. Cell nuclei were counterstained in haematoxylin, and sections were mounted in Aquamount aqueous mountant (BDH, Poole, UK). Regions of probe annealing were observed as a brown precipitate.

Positive control slides were prepared by fixing HT1080 tumour cells on to coverslips and treating them in the same

way as tissue sections. Negative control sections were either treated without probe, or were pretreated with ribonuclease (RNase) H (10 mg/ml in Tris-hydrochloric acid 100 mmol/l, pH 7.5, magnesium chloride 100 mmol/l) by incubating them at 37°C for 1 h. *In situ* hybridization was then carried out as described above.

In situ zymography

Sections (10 µm) were cut from frozen tissue specimens and applied to silane-coated microscope slides. The slides were submerged in prewarmed (37°C) fluoresceinated porcine gelatin (Molecular Probes, Leiden, Netherlands; 4 µg/ml in Tris-hydrochloric acid 50 mmol/l, pH 7.6, calcium chloride 5 mmol/l, sodium azide 0.2 mmol/l) for 18 h at 37°C. The reverse side of the slide was then wiped dry.

Negative controls were prepared by including 1,10-phenanthroline 10 mmol/l or EDTA 50 mmol/l within the gelatin solution. Positive control slides were pretreated with phorbol 12-myristate 13-acetate 200 nmol/l for 30 min at 25°C. Excess pretreatment solution was drained and the slides were carefully rinsed with PBS before incubation.

Gelatinolysis was visualized by viewing the slides under mercury vapour lamp illumination (360 nm) and appeared as green fluorescence against a dark background. By comparison with sections illuminated by white light, the precise location of proteolytic activity was determined.

Results

To maintain consistency in figures, sections were illustrated with the adventitial layer on the left side, with the media the main focus of attention. Haemotoxylin and eosin-stained sections of control and aneurysm aorta demonstrated that

control tissue was highly organized, with intact intimal, medial and adventitial layers. SMC nuclei were visible in the medial layer, as were the nuclei of fibroblasts and sparse inflammatory cells in the adventitia. The aneurysm tissue was disorganized and comparatively acellular, with few SMCs and a prominent inflammatory infiltrate which localized to dense patches within the media and adventitia. Elastin van Gieson-stained sections (Fig. 1) further revealed the degenerative changes characteristic of AAA. The control aorta exhibited intact elastin and collagen fibres, with prominent SMCs all within the medial elastic lamellae. In contrast, the AAA tissue had profoundly fragmented elastin, visibly reduced collagen fibre and SMC numbers, and a thinned medial layer, which was not distinctly identifiable. Medial and adventitial inflammatory cells were also visible, as was the thickened adventitia, which contained numerous vasa vasorum.

Immunohistochemical studies

More specific detail of these changes was visible when staining immunohistochemically for specific cell types. The reduction in the number of SMCs in AAAs was demonstrated by the use of an antismooth muscle actin antibody (Fig. 2). A broad band of reactivity, associated with the medial elastic lamellae, was seen in the control aorta. Strong staining was also associated with the adventitial vasa vasorum, reflecting the presence of SMCs in those vessels. AAA tissue showed markedly reduced reactivity in the media, which was thinned. The influx of inflammatory cells was also clearly defined by the use of antimacrophage antibody. Little or no reactivity was detected in the control aorta, in contrast to the AAA tissue, where macrophages were present in dense patches within the medial and

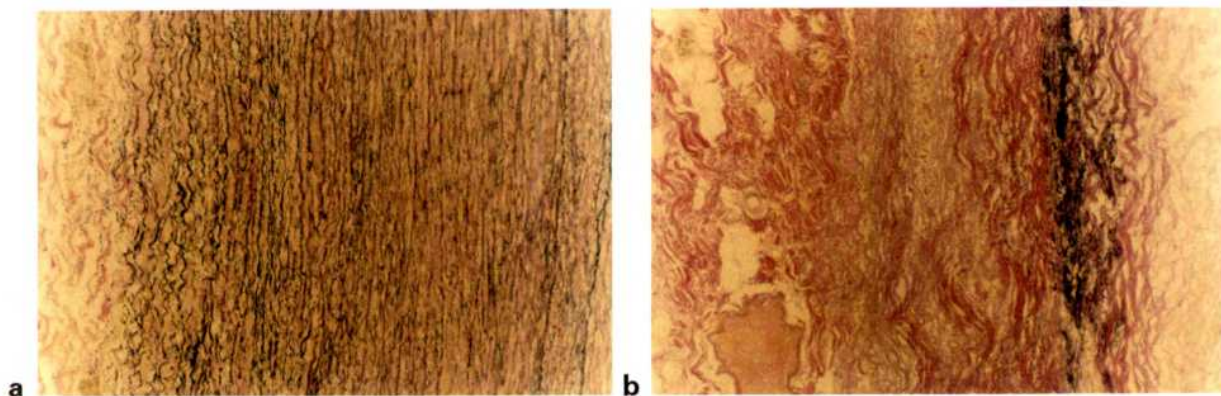


Fig. 1 Micrographs of elastin van Gieson-stained sections of **a** control aorta and **b** aortic aneurysm, illustrating the intact intimal medial and adventitial layers of the former, and the relative destruction and disorder of the latter, associated with a loss of elastin and smooth muscle cells (original magnification $\times 160$)

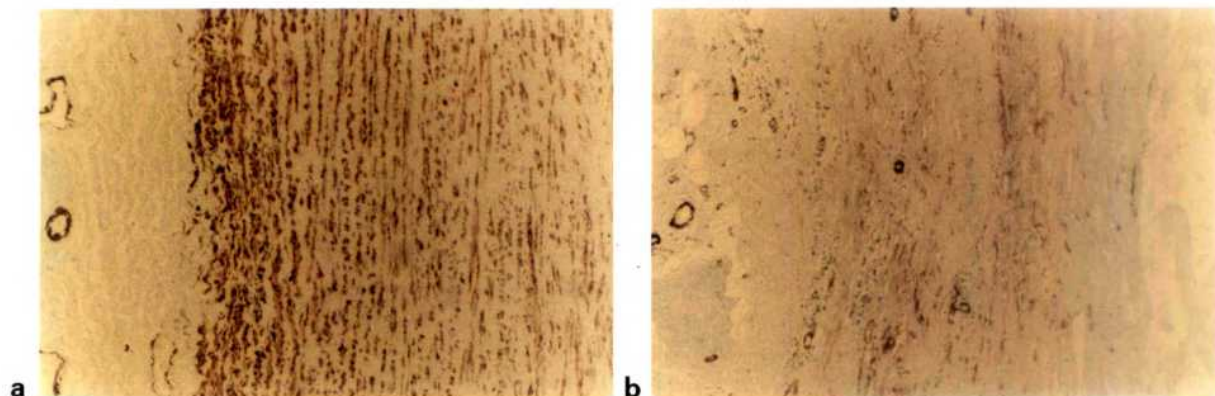


Fig. 2 Micrographs of aortic tissue stained for α smooth muscle actin by immunohistochemistry. **a** Control aorta and **b** aortic aneurysm, illustrating the presence of smooth muscle cells (SMCs) in the medial layer and vasa vasorum of the control artery, in contrast to the aneurysmal vessel in which SMCs are sparse and confined to a narrow medial band (original magnification $\times 160$)

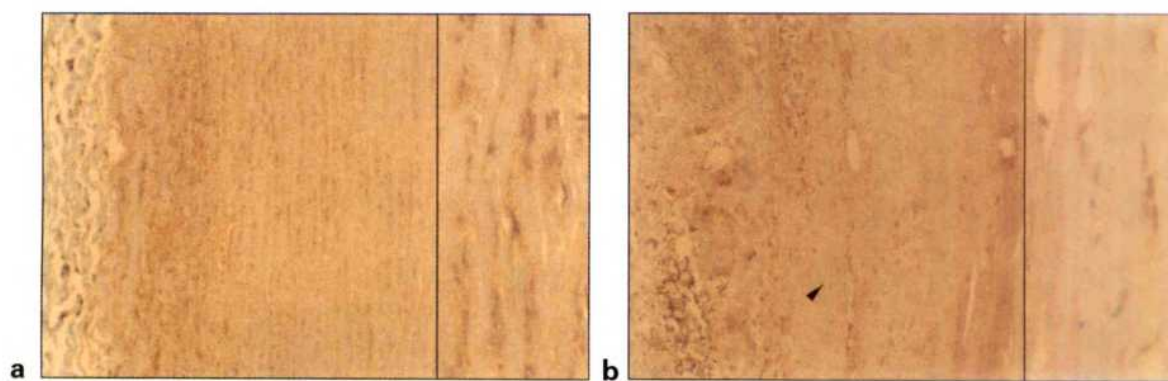


Fig. 3 Micrographs of aortic tissue stained for matrix metalloproteinase (MMP) 2 by immunohistochemistry. **a** Control aorta and **b** aortic aneurysm, illustrating the production of MMP-2 by medial smooth muscle cells (arrowed) in both tissues and infiltrating leucocytes in the latter (original magnification $\times 160$ and $\times 320$)

adventitial layers. This infiltrate may consist of both macrophage and lymphocyte activity, and the density of their appearance perhaps suggests the formation of lymphoid follicles, which may imply an ongoing cellular immune response.

Other groups have attributed much of the ECM-degrading activity present in AAA tissue to the inflammatory cells. The present work confirmed that infiltrating leucocytes produced MMP-2, MT1-MMP and TIMP-2. However, other cells were shown to be capable of producing the same proteins described above, in particular the medial SMCs (Figs 3 and 4). In the media of control aorta, MMP-2 and MT1-MMP were detected, along with TIMP-2. These were located diffusely within the medial layer, but were particularly concentrated towards the adventitial aspect and to a lesser extent in the adventitial layer. In AAA tissue, the relative lack of SMCs revealed a reduction in MMP reactivity, although they were also shown to produce MMP-2, MT1-MMP and TIMP-2. Background staining

for MMP-2 in aneurysm tissue was high, possibly reflecting the inflamed state of the artery and binding of excess enzyme to the matrix.

In situ hybridization

The production of MMP-2 has previously been localized³⁷, but no studies to date have examined the production or expression of MT1-MMP in vascular tissue of any kind. In the present study, the use of *in situ* hybridization permitted a precise cellular source to be defined for MMP-2–MT1-MMP and TIMP-2 expression, in order to clarify further the involvement of this system in the development of AAA. In control aorta, MMP-2, MT1-MMP (Figs 5 and 6) and TIMP-2 were expressed by medial SMCs. The contrast in AAA tissue was marked; the signal for MMP-2 was less widespread because of the reduced numbers of SMCs, yet strong where cells remained. It was also notably strong in the inflammatory cells of the medial and adventitial layers.

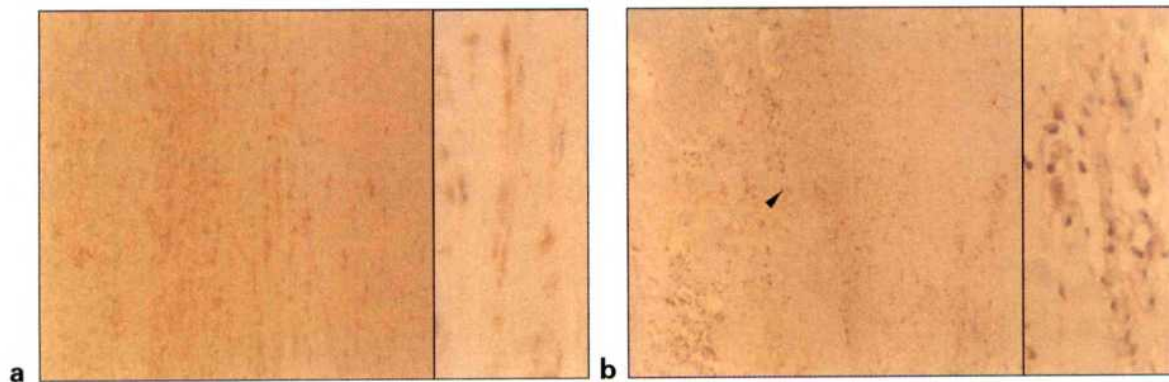


Fig. 4 Micrographs of aortic tissue stained for membrane type 1 matrix metalloproteinase (MT1-MMP) by immunohistochemistry. **a** Control aorta and **b** aortic aneurysm, illustrating the production of MT1-MMP by medial smooth muscle cells (arrowed in abdominal aortic aneurysm) in both tissues (original magnification $\times 160$ and $\times 320$)

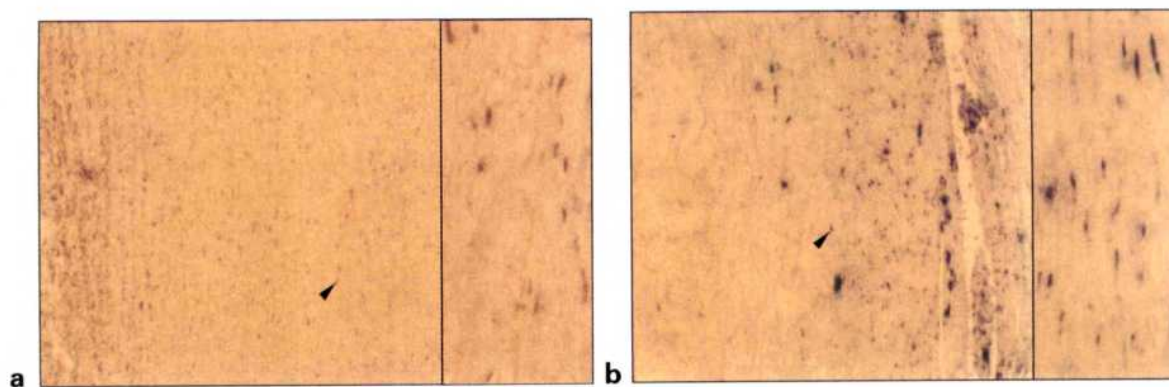


Fig. 5 Micrographs of *in situ* hybridization treated sections of **a** control aorta and **b** aortic aneurysm, probed for matrix metalloproteinase (MMP) 2. Both expressed MMP-2 in their smooth muscle cells (SMCs; arrowed). In control aorta this was detected diffusely within the medial layer; in aneurysm tissue the signal was confined to a narrow band corresponding to the location of the remaining SMCs (original magnification $\times 160$ and $\times 320$)

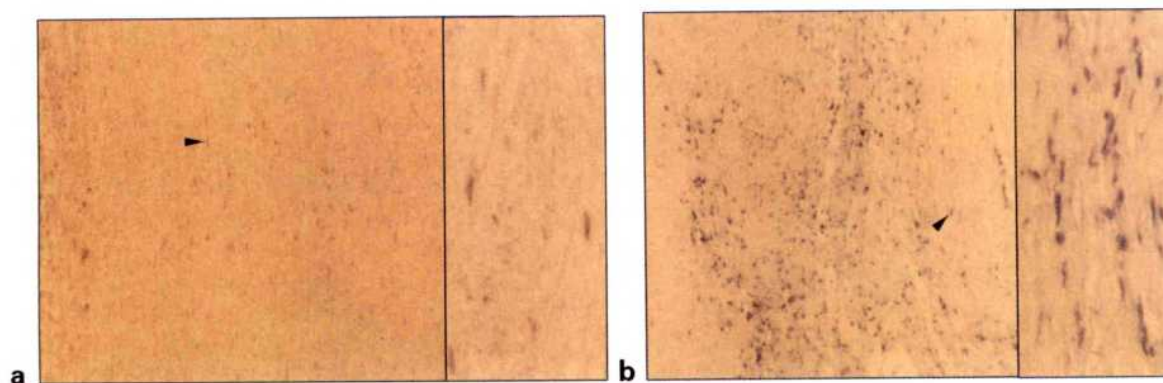


Fig. 6 Micrographs of *in situ* hybridization treated sections of **a** control aorta and **b** aortic aneurysm, probed for membrane type 1 matrix metalloproteinase (MT1-MMP). Both expressed MT1-MMP in their smooth muscle cells (SMCs; arrowed). As above, signal was detected diffusely within the medial layer in control artery, and confined to a narrow band corresponding to the location of the remaining SMCs in the aneurysmal vessel (original magnification $\times 160$ and $\times 320$)

The TIMP-2 signal was similarly expressed in the medial SMCs, and was also seen in infiltrating cells of the media and adventitia. It was further associated with adventitial vasa vasorum. The probe for MT1-MMP produced a high level of signal in the medial SMCs of AAA tissue, and was also strong in the infiltrating cells of the media and adventitia.

Confirmation of probe binding was tested by application of the MMP-2, MT1-MMP and TIMP-2 probe cocktails to fixed HT1080 cells. This revealed reactivity in the perinuclear region, indicating that expression of all three gene transcripts was detectable. In all cases, the reactivity demonstrated by *in situ* hybridization was abolished by treatment of the sections with RNase H, and was also absent when the protocol was carried out without probe.

In situ zymography

The images produced revealed the site of gelatinolytic enzyme activity in the tissue sections of control and aneurysmal aorta. Fig. 7 illustrates a typical result produced by sections of control and aneurysmal aorta. Control aorta exhibited diffuse gelatinolysis within the medial layer, which was particularly associated with the elastin fibres. This activity was abolished in the 1,10-phenanthroline- and EDTA-treated sections, suggesting its identity as a metalloproteinase. Positive control slides revealed a moderate general increase in fluorescence, indicating that a small amount of latent MMP was present within the tissue. Again, this activity was associated mainly with the elastin

fibres and was also present in the adventitial layer around the vasa vasorum.

The aortic aneurysm tissue also contained gelatinolysis within the medial and adventitial layers, but the distribution of this reflected the disorganization of the vessel wall architecture. Medial fluorescence was reduced to a thin band, co-localizing with the elastin as illustrated earlier in the elastin van Gieson sections. Adventitial fluorescence was limited, and associated with the inflammatory cells. This activity was also abolished by treatment with 1,10-phenanthroline. Positive control slides again indicated that a proportion of MMP within the aneurysm tissue was latent, its distribution matching that of the active enzyme.

Discussion

Aneurysmal degeneration of the arterial wall appears to be a process that is predominantly localized to the media and adventitia. One of the primary differences between aneurysm and atherosclerotic tissue is the fragmentation and destruction of elastin tissue in the arterial media of the former^{5,11,12,38,39}. This elastolytic process is observed early in aneurysm formation and may be the crucial step in aneurysm pathogenesis. Hypothetically, degradation of medial elastin could be the catalyst for the widespread biochemical and pathological changes observed in aneurysm vessels¹⁴. Degradation of elastin releases elastin-derived peptides, which are potent chemoattractants for leucocytes and appear to promote increased

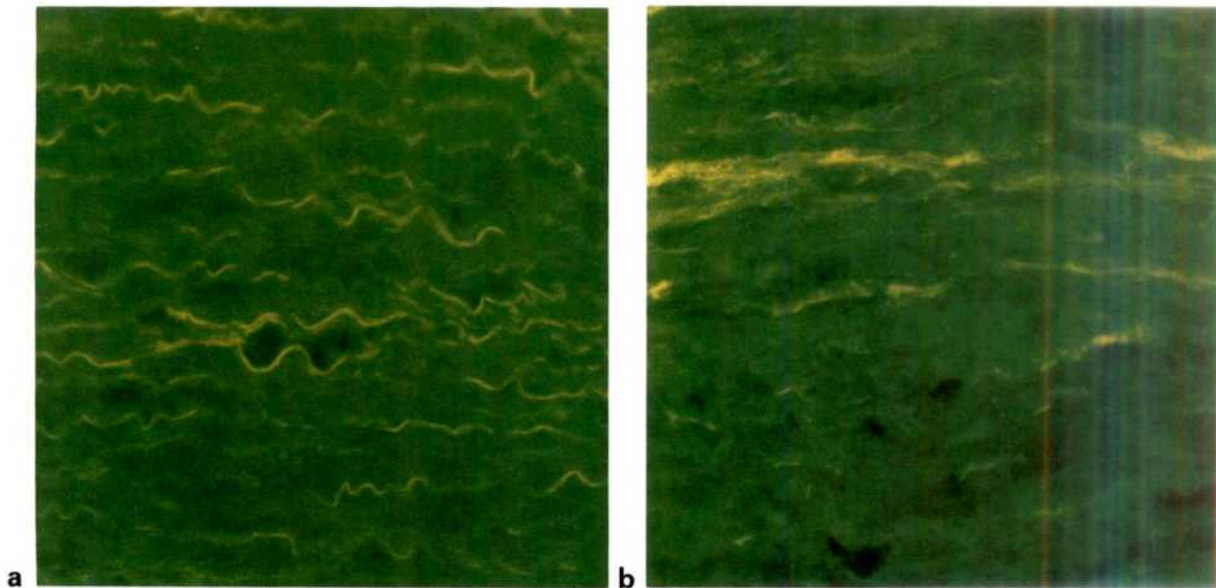


Fig. 7 Micrographs of *in situ* zymography using **a** control aorta and **b** aortic aneurysm. Green fluorescence indicates regions of gelatinolysis, which were confined in both tissues to the elastin fibres. Enzyme activity was not localized to specific cell types using this technique (original magnification $\times 320$)

production of MMPs by resident mesenchymal cells in the arterial wall^{40–42}. Enhanced production of proteolytic enzymes by infiltrating leucocytes and resident SMCs may then initiate further elastin degradation in a cascade reaction, leading to the widespread matrix remodelling observed in established aneurysms.

Recently, several studies have suggested that raised levels of MMP-2 might be responsible for medial elastin degradation in the aneurysm wall. Crowther *et al.*²¹ demonstrated increased levels of MMP-2 production from SMCs derived from the wall of aortic aneurysms compared with cells cultured from atherosclerotic lesions. Similarly, Patel *et al.*²² observed that aneurysm-derived SMCs had greater elastolytic activity than cells from age-matched aortic tissue. Both of these studies used tissue culture techniques to isolate the SMCs and to maintain them in an environment free from the cytokinetic influences present in the aneurysm wall. The observations described in these experiments may therefore reflect primary differences between the aneurysmal and atherosclerotic processes. Further support for an aetiological role for MMP-2 was suggested by data from Freestone *et al.*²³, who demonstrated that the dominant elastolytic enzyme in small aneurysms was MMP-2, with MMP-9 assuming more importance as the aneurysm diameter increased and leucocyte infiltration became more dense.

Contemporary evidence therefore suggests an important role for MMP-2 in the genesis of AAA. However, like all members of the MMP family, the activity of MMP-2 is tightly regulated in the extracellular compartment⁴³, and to date little attention has been directed towards the presence of the inhibitors and activators of MMP-2 within the arterial wall. Studies on these enzymes are crucial towards the understanding of aneurysm pathogenesis, as MMP-2 does not act in isolation but forms a tightly regulated system of elastolysis along with MT1-MMP and TIMP-2.

The present study has demonstrated that MT1-MMP and TIMP-2 are both present in the aneurysm and control arterial wall in the same distribution as MMP-2. MMP-2 has previously been localized to the media of both aneurysm and atherosclerotic tissue^{23,43–45}, and is known to be produced by the mesenchymal cells of the arterial wall⁴³. Similarly, TIMP-2 has been found in the media of atherosclerotic and aneurysmal arteries^{44,45}. It is significant in the present study that MT1-MMP was demonstrated in the medial SMCs of both aneurysm and control tissue, as it may provide a mechanism to activate MMP-2 in the arterial wall.

Although MT1-MMP has been described as localizing MMP-2 to the cell surface, no specific membrane staining was detected. This suggests that all MMP-2–MT1-MMP complexes had been cleaved from their cell membrane-

bound site, perhaps reflecting a postactivation state. Some authors have suggested that the cleaved form of MT1-MMP correlates most closely with activation of MMP-2⁴⁶. It is possible that this may be shown to be consistent with the late stage of disease.

An important point to note was the lack of leucocytes in the medial layer of control aortic tissue. The absence of inflammatory cells from these specimens suggested that their presence in AAAs was likely to be a secondary phenomenon following an initial trauma. There was little evidence to support the view that leucocytes may be responsible for such an event, and this may strengthen the argument that the resident SMCs are the most likely source of proteases causing damage to the vessel wall in the first instance.

Also shown was the MMP activity within the control and aortic aneurysm wall, as visualized by *in situ* zymography. The use of *in situ* zymography was a previously untried method of analysis of protease activity in the aortic wall. Few reports of this technique exist, being confined to those from Galis *et al.*⁴⁷ and Mungall *et al.*⁴⁸. The technique allows differentiation between latent and active forms of MMPs, information denied by the use of immunohistochemistry and *in situ* hybridization. However, the major drawback is the requirement for frozen tissue. Freezing is associated with a reduction in the microscopic integrity of tissue architecture, which is better preserved in formaldehyde-fixed, paraffin wax-embedded specimens.

The identification and localization of MMPs and TIMPs by specific antibody or probe binding was augmented by *in situ* hybridization demonstration of active enzyme associated with the elastin fibres. By interpolation from immunohistochemical analysis, this activity was most likely to represent active MMP-2, both in control and aortic aneurysm tissue, as no other gelatinolytic MMP was consistently localized to the SMCs of the medial layer. Thus, their secreted MMP-2 may be activated by MT1-MMP in complex with TIMP-2, causing fragmentation of elastin and the initiation of a proteolytic inflammatory reaction, leading to aneurysm degeneration.

The present study provided evidence that all components of the MMP-2–MT1-MMP–TIMP-2 system are present in the media of large vessels. These observations support the concept of a pivotal role for MMP-2 in the medial elastolysis that accompanies aneurysm formation, and may indicate that control of the activator, MT1-MMP, is an important mechanism determining net proteolysis.

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Factors influencing the functional outcome of restorative proctocolectomy in ulcerative colitis

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Background: Restorative proctocolectomy is considered to be the procedure of choice in the operative treatment of ulcerative colitis. The aim of this study was to evaluate the functional outcome following operation and to identify possible predictive factors.

Methods: Some 168 patients (median age 32 years, 102 men) with ulcerative colitis underwent restorative proctocolectomy. The functional outcome was evaluated by a symptom index created from a questionnaire at a median of 29 (13–123) months of follow-up. The records of these patients were reviewed, and preoperative, peroperative and postoperative variables were registered and related to outcome.

Results: The response rate to the questionnaire was 155 (92 per cent) of 168. The symptom index was related to patients' overall assessment of outcome. In spite of a perceived good result many patients experienced a number of symptoms. Age over 50 years ($P < 0.01$), presence of extraintestinal manifestations ($P < 0.05$) and late complications, such as anastomotic stricture ($P < 0.05$), pouchitis ($P < 0.01$) and anal pain ($P < 0.05$), were related to a less favourable outcome.

Conclusion: While preoperative data may help in selecting patients suitable for restorative proctocolectomy, prevention of late complications seems most important in improving the functional outcome.

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Introduction

Restorative proctocolectomy has become an established surgical treatment of ulcerative colitis. Since the initial description of the ileal pouch–anal anastomosis by Parks and Nicholls¹, several modifications of the technique have been proposed, such as different pouch designs^{2–5} and the use of staplers^{6,7}. Mortality rates after ileal pouch–anal anastomosis now approximate zero but postoperative morbidity is still high^{8–10}.

Ulcerative colitis is a benign disease and proctocolectomy is intended to be curative. Many of these patients are young and have a long life expectancy. With these perspectives, the results of reconstructive pouch surgery are now focused on functional outcome. Patient satisfaction with the ileal-pouch procedure has been reported to be high and the overall outcome classified as good or excellent by 70–90 per cent of patients^{11,12}. Definite pouch failure necessitating pouch excision or a defunctioning stoma is the final result in 4–19 per cent of operations^{8,13}. However, patients with a functioning pouch and a good overall result may experience

various continuous or episodic symptoms. Variables such as postoperative stool frequency, urgency of defaecation and faecal continence are important measures of outcome; however, analysis of other symptoms might give extra information. Therefore, an index of symptoms, as used by some authors¹⁴, might be a valuable tool when evaluating the functional outcome after pouch surgery.

The aim of this study was to evaluate the functional outcome of ileal pouch–anal anastomosis for ulcerative colitis with a symptom index created from a questionnaire. A second aim was to identify possible predictors of outcome from preoperative and postoperative data.

Patients and methods

Patients

One hundred and eighty-four patients with ulcerative colitis had restorative proctocolectomy during the time period 1983–1996. Records of these patients were studied with respect to preoperative, peroperative and postoperative

data. Twelve patients had had their reservoir excised, two patients had died and two further patients were diagnosed postoperatively with Crohn's disease, leaving 168 patients for follow-up. There were 102 men and 66 women with a median age of 32 (range 16–68) years. The diagnosis of ulcerative colitis was established 84 (5–432) months before surgery and was based on clinical, endoscopic and histopathological criteria. One hundred and two patients had had a colectomy performed previously (56 as an emergency operation).

Operative procedures and complications

All patients had preoperative bowel preparation including rectal washout and all received prophylactic antibiotics. The first two ileal reservoirs were constructed as a lateral isoperistaltic pouch (H pouch)⁴. A handsewn S reservoir ($n=89$) was most common in the early half of the series whereas a stapled J reservoir ($n=77$) was most frequent in the later part. The ileal pouch–anal anastomosis was handsewn in 99 patients and constructed with a double-stapling technique in 69 patients. Mucosectomy was performed in 99 patients. A covering loop ileostomy ($n=119$) was used routinely in the first half of the series whereas in later years a loop ileostomy was used in selected patients. Eight surgeons performed the pouch surgery although the majority of operations ($n=118$) were carried out by two surgeons. One of four senior consultants was present during all operations.

Early morbidity was defined as follows: (1) bleeding, necessitating reoperation; (2) anastomotic leak, causing symptoms and verified by endoscopy and/or contrast enema; (3) abscess, diagnosed with computed tomography or ultrasonography; (4) fever, defined as a temperature of 38°C or more from day 7 without an apparent cause; and (5) wound infection requiring local drainage. Other, not directly procedure-related, complications were also recorded, e.g. venous thrombosis, pulmonary and urinary tract infections. Long-term complications, fistulas (pouch–vaginal, pouch–perianal including sinuses in relation to the anastomosis), anastomotic stenosis (requiring one or more dilatations but not including dilatation at closure of the loop ileostomy), pouchitis (clinical and endoscopic diagnosis), intestinal obstruction (operative treatment), incisional hernia and persisting anal pain (not clearly related to other pouch–anal complications) were recorded from patient records. All patients in the series were followed at 3–6-month intervals during the first 2 years and then yearly or on patient demand. Thirty-one of the patients participated in a double-blind randomized study evaluating allopurinol as a prophylactic agent against the development of pouchitis.

Questionnaire

The 168 patients available for follow-up constituted the study group and were sent a questionnaire consisting of 27 items. Seventeen of the questions requested a graded answer whereas ten were of a dichotomous type. Each of these questions was scored ranging from 0 to 4 (ten questions), 0–5 (one question), 0–6 (six questions), 0–8 (three questions) and 0–10 (seven questions). From the sum of scores in all questions (1–19) an index was created which ranged from 0 (symptom free) to a maximum of 175 (*Appendix 1*). Patients were also asked to evaluate the overall outcome of surgery, if they would recommend the operation to a relative, if they would have undergone the operation with knowledge of their outcome or if they had preferred the outcome with a primary ileostomy.

Statistical analysis

Values are median (range) unless otherwise stated. Correlations were studied with Spearman rank correlation test. Kruskal–Wallis and Mann–Whitney *U* test were used to compare groups and Fisher's exact test was used to compare proportions. Multiple regression analysis was also used to delineate independent variables related to functional outcome. All *P* values are two-tailed and $P<0.05$ was considered significant. Statistica[®] software (StatSoft, Tulsa, Oklahoma, USA) was used for the calculations.

Results

Functional results

One hundred and fifty-five patients answered the questionnaire (response rate 92 per cent) at a median of 29 (range 13–123) months after the operation. Follow-up was 2 years or more for 90 per cent of the patients. Daytime stool frequency was five or less in 74 per cent of patients (*Table 1*). Night time stool frequency and urgency of defaecation are also documented in *Table 1*. Difficulty in evacuation was experienced by 31 patients (20 per cent). Five patients sometimes used a catheter to assist evacuation. The majority of patients (74 per cent) had perfect daytime continence. Regular nocturnal incontinence was reported by 30 per cent of patients (*Table 2*). Fifty-four patients used loperamide regularly or periodically to modify stool frequency whereas 87 patients managed without any medication. The majority of patients ($n=119$, 77 per cent) had not undertaken any dietary restrictions whereas 26 used a fat-reduced regimen and ten avoided certain food ingredients.

About one-third of patients experienced episodes of abdominal pain. Anal pain and pain related to defaecation were not uncommon, although few patients had symptoms on a daily basis (Table 3). The overall situation did have some impact on the working situation ($n = 41$, e.g. change of work), on travelling and vacations ($n = 41$, e.g. stopped mountain trekking) and on social activities ($n = 27$, e.g. necessity of a nearby toilet).

The overall outcome of surgery was classified as excellent by 77 patients (50 per cent), good by 50 patients (32 per cent), fair by 21 (14 per cent) and poor by six (4 per cent). No one stated a very poor result. Six patients would not have undergone surgery with knowledge of the outcome, four of whom had a poor outcome whereas two claimed a good result. A primary ileostomy would have been preferred by three of these patients (all with a poor outcome) whereas three were hesitant. Three patients (2 per cent) would not recommend the operation to a relative.

Table 1 Stool frequency and urgency of defaecation in 155 patients with ulcerative colitis after ileal pouch–anal anastomosis

	No. of patients
Daytime stool frequency	
<2	4 (3)
2–4	65 (42)
5	46 (30)
6–8	37 (24)
>8	3 (2)
Night time defaecation	
Never/rarely	36 (23)
Monthly	27 (17)
Weekly	53 (34)
Every night	39 (25)
Urgency of defaecation	
<5 min	8 (5)
5–15 min	16 (10)
15–30 min	22 (14)
>30 min	109 (70)

Values in parentheses are percentages

The calculated symptom index ranged between 2 and 23 (median 28) (Fig. 1). The index was closely related to the patients' overall classification of outcome (Fig. 2).

Associations with outcome

There was a weak overall correlation between age and symptom index ($r = 0.20$, $P = 0.01$). Patients aged over 50 years ($n = 16$) had a median symptom index of 54 (3–123) compared with 27 (2–108) in younger patients ($P = 0.008$). There was a tendency towards a lower symptom index in men than in women (27 (2–116) versus 35 (3–123); $P = 0.09$). Among women, the 15 nulliparous women had a lower symptom index than the parous women, but the difference did not reach statistical significance (25 (3–36) versus 38 (6–123); $P = 0.10$). The duration of antecedent ulcerative colitis and the extent of disease did not influence outcome. Patients with extraintestinal manifestations ($n = 19$) had a worse functional outcome than patients without (45 (2–123) versus 26 (2–116); $P = 0.04$).

The individual surgeon or consultant influenced operating time and operative blood loss (data not shown) but there were no differences regarding postoperative complication rate or functional outcome. There were some fluctuations in symptom index when analysed overall each year, but there were no statistically significant differences. The different pouch designs, types of anastomosis and other variations in the surgical technique did not affect the symptom index.

There were 48 early procedure-related complications in 39 patients. In addition there were 16 other complications in 15 patients (pulmonary embolus, venous thrombosis, transient nerve palsy, urinary tract infection, decubitus ulcer, etc.). One hundred and one patients had no post-operative complications. Early procedure-related morbidity had no impact on symptom index. Late morbidity was registered as 100 complications in 84 patients. In a univariate analysis, pouchitis (index 47 (14–116) versus 25

Table 2 Faecal incontinence and use of pads following ileal pouch–anal anastomosis in 155 patients with ulcerative colitis

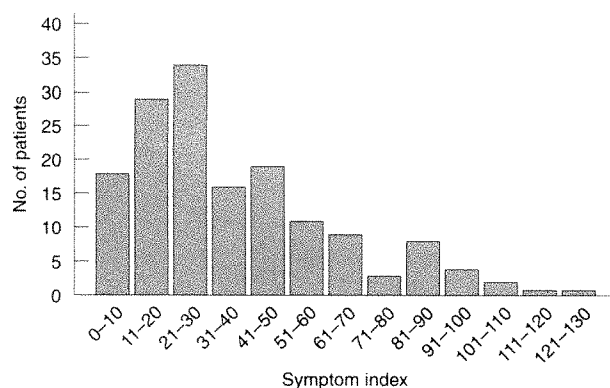
	Incontinence episodes and use of pad				
	Never	Rarely	Monthly	Weekly	Daily
Daytime					
Gas*	107 (69)	11 (7)	24 (16)	7 (5)	5 (3)
Stools	115 (74)	16 (10)	6 (4)	13 (8)	5 (3)
Use of pad	125 (81)	2 (1)	4 (3)	6 (4)	18 (12)
Night time					
Stools	73 (47)	34 (22)	23 (15)	19 (12)	6 (4)
Use of pad	115 (74)	3 (2)	4 (3)	11 (7)	22 (14)

Values in parentheses are percentages. *Data missing for one patient

Table 3 Frequency of abdominal and perianal pain in 155 patients with ulcerative colitis following ileal pouch–anal anastomosis

	Episodes of pain				
	Never	Rarely	Monthly	Weekly	Daily
Abdominal pain	102 (66)	15 (10)	22 (14)	10 (6)	6 (4)
Painful defaecation	122 (79)	14 (9)	11 (7)	7 (5)	1 (1)
Perianal pain*	110 (71)	13 (8)	15 (10)	11 (7)	5 (3)

Values in parentheses are percentages. *Data missing for one patient

**Fig. 1** Distribution of symptom index in 155 patients operated with an ileal pouch–anal anastomosis for ulcerative colitis after a median of 29 months' follow-up

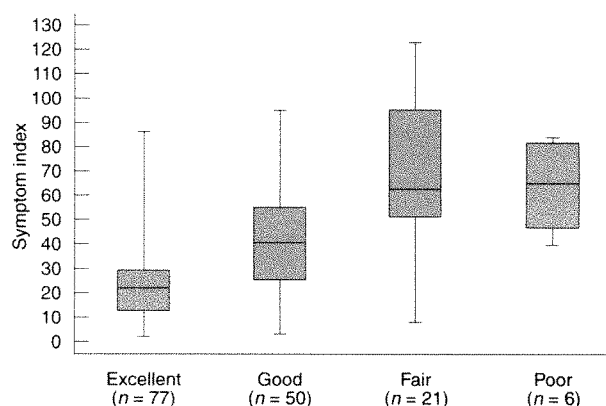
(2–123); $P=0.003$), anastomotic stenosis (42 (3–105) *versus* 26 (2–123); $P=0.02$) and anal pain (62 (16–108) *versus* 28 (2–123); $P=0.01$) were related to a less favourable outcome (Fig. 3). One patient had retrograde ejaculation and another had urinary bladder dysfunction.

A multiple regression analysis of 29 preoperative (e.g. sex, age, extension and duration of disease), peroperative (e.g. operating time, bleeding, surgeon, reservoir type, etc.) and postoperative (early and late complications) variables was performed. In this analysis, age ($P=0.004$), extraintestinal manifestations ($P=0.006$), pouchitis ($P=0.003$), anal pain ($P=0.001$) and anastomotic stenosis ($P=0.005$) were independently related to symptom index. Length of follow-up was not correlated to symptom index.

Non-evaluated patients

Thirteen patients did not answer the questionnaire. They were younger than the responding group (24 (16–51) *versus* 33 (16–68) years; $P<0.001$). Otherwise there were no significant differences between responders and non-responders with respect to the variables studied.

Twelve patients had the pouch excised before follow-up. The immediate reason for excision was pouchitis in five

**Fig. 2** Relationship between patients' global categorization of outcome after ileal pouch–anal anastomosis and symptom index evaluated from a questionnaire ($P<0.00001$, Kruskal–Wallis test)

patients, anastomotic stricture in three and poor functional outcome in four. Altogether, five of these patients had eight early complications and nine patients had 15 late complications. Preoperative variables as age, sex, duration and extension of colitis, presence of extraintestinal manifestations or steroid medication did not differ from those in patients with an intact pouch. However, 11 of these 12 patients had mucosectomy performed and a handsewn anastomosis compared with 101 of 170 in all other patients ($P=0.03$, Fisher's exact test).

Two patients (men) had died at time of follow-up from unrelated causes. Two patients developed Crohn's disease, in one of whom the ileal pouch was removed.

Discussion

In this study the functional outcome after ileal–anal pouch surgery has been related to preoperative, peroperative and postoperative factors that could influence the postoperative result. The pouch excision rate was 12 (7 per cent) of 182 in all patients with ulcerative colitis which is in agreement with previous reports^{8,15}. There were no patients with a defunctioning stoma. Six patients reported a poor functional outcome in the questionnaire giving an overall failure

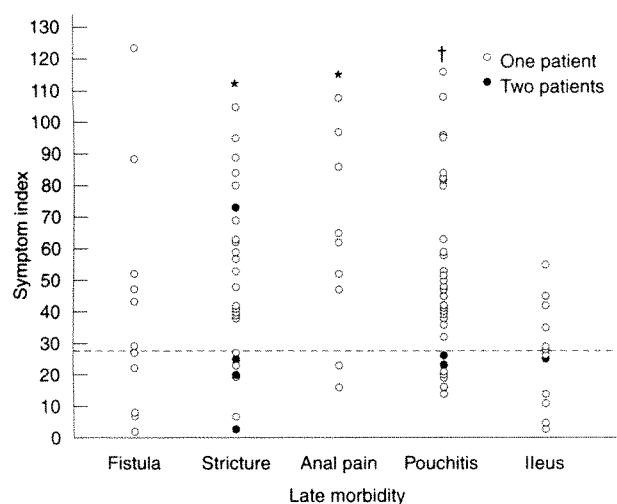


Fig. 3 Relationship between late complications after ileal pouch-anal anastomosis and functional outcome as expressed by symptom index. The dotted line indicates the median symptom index of all 155 patients. * $P < 0.05$, † $P < 0.01$ (univariate analysis; Mann-Whitney U test)

rate of 10 per cent for the ileal pouch procedure. The total early morbidity rate (major and minor) was 35 per cent. These figures are similar to those reported in other studies^{8,11,16}.

The questionnaire used to evaluate outcome focused on continence, stool frequency and urgency of defaecation which are important factors contributing to the functional result. Questions about medication, diet, working situation, social activities and travelling are, to various degrees, dependent on these variables but still add information about the patients' overall quality of life. The symptom index created from the questionnaire correlated with the patients' global assessment of outcome. Data from this questionnaire could be used to calculate the index described by Öresland *et al.*¹⁴ and the correlation between the indices was good ($r = 0.92$, $P < 0.01$). The distribution of the symptom index showed a wide range. It was also apparent that patients who were satisfied with the pouch operation, and classified the result as excellent or good, still experienced a number of symptoms.

In the present study, age was a significant predictive factor of outcome. This is in contrast to some previous reports^{17,18}. A possible explanation is that a symptom index may identify trends which will not be statistically significant when symptoms are analysed individually. The present results support the findings by Öresland *et al.*¹⁴ who also found age to be a relevant factor when measuring outcome by a symptom index. However, 11 of the 16 patients aged over 50 years stated an excellent or good result, so age *per se*

should not exclude patients from having an ileal pouch but rather be a part of the preoperative evaluation.

The presence of extraintestinal manifestations of ulcerative colitis was another preoperative variable with predictive value with respect to functional outcome. Sclerosing cholangitis has been related to an increased incidence of postoperative complications^{19,20} and also to increased risk of developing pouchitis²¹. Other manifestations, such as arthritis, eye and skin complications, are also related to an increased risk of pouchitis²². In this study, pouchitis had a strong relation to a high symptom index and this may in part explain the association between extraintestinal manifestations and index. However, the multiple regression analysis showed that these variables were independently related to a higher index. To what extent the presence of extraintestinal manifestations should influence the choice of surgical treatment is unclear. Further studies are required to address this issue.

The J-shaped reservoir has become the most used pouch design. This design combined with a double-stapling technique has been associated with fewer complications and a better outcome^{23,24}. Mucosectomy and S-type reservoirs were associated with pouch failure in the total series. Follow-up for the S pouches was longer but most pouch excisions were done within two years of construction. In patients with an intact pouch, the design and type of anastomosis did not affect the symptom index. All major evacuation difficulties were seen in patients with an S or H pouch design. This necessitated revision with shortening of the efferent limb ($n = 2$) and reduction of pouch volume ($n = 2$) in four patients with an S reservoir.

Early complications following surgery were not predictive of later outcome as evaluated by the symptom index. The incidence of some of the complications was low and definite conclusions are difficult to make. The anastomotic leak rate was 12 (8 per cent) of 155 but in this group of patients only one developed a late complication. About half of the patients with early infectious complications such as abscesses and postoperative fever developed late complications. Patients with early septic complications seemed to function as well as other patients. Thus, the sequence of pelvic sepsis followed by fibrosis and subsequent poor function was not in general applicable in this series of patients with functioning reservoirs.

Among late complications pouchitis was the most frequent (21 per cent) and was also clearly related to a worse outcome. The cumulative incidence of pouchitis increases with time and may have affected nearly half of the patients by 10 years of follow-up¹⁵. A consequence might be a deterioration of overall functional outcome with time but no correlation was found between time of follow-up and symptom index in the present study. Differences in

diagnostic criteria of pouchitis and thereby variations in incidence may be one explanation, while different forms of pouchitis may have a different clinical course and impact on pouch function²⁵. Anastomotic stricture was nearly as common as pouchitis and was also related to an increased symptom index. In six of 29 patients the stricture was related to preceding pelvic sepsis; otherwise the aetiology of the stricture was unclear. There was no acute postoperative pouch ischaemia but impaired circulation is one probable cause of stricture. Likewise, the cause of anal pain was unclear. Low-grade mucositis, cuff infection or fissure were possible causes although this was not evident at examination. These patients were treated with antibiotics and local steroids, with acceptable symptom control.

In conclusion, patients with a subjective excellent or good overall outcome following restorative colectomy still experience a number of symptoms. Age and presence of extraintestinal manifestations are variables related to a less favourable outcome but do not exclude pouch surgery. These factors may help in selecting patients for an ileal reservoir. From the surgical viewpoint, the main challenge seems to be how to reduce late complications, especially pouchitis, in order to improve functional outcome.

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Appendix 1 Questionnaire for patients operated for ulcerative colitis

Please answer the following questions with an × for the alternative that is most appropriate to you. The answer should correspond to your perception of the situation over the past month. After some questions and at the end of the questionnaire there is room for comments to the questions and the questionnaire as a whole.

1. How often do you pass a motion in day time?

< 2 times/day	2–4 times/day	5 times	6–8 times/day	> 8 times/day
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2. How often do you pass a motion during the night?

< Once/month	Once/month–once/week	> Once/week–once/night	> Once/night
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3. For how long can you defer a visit to the toilet when you feel an urgent need of defaecation?

> 30 min	30–15 min	< 15–5 min	< 5 min
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4. How often do you experience disturbing urgency (need to urgently visit the nearest toilet)?

< Once/month	Once/month–once/week	Once/week–once/day	> Once/day
--------------	----------------------	--------------------	------------
5. Do you at any time have difficulties with bowel evacuation (need to sit at the toilet for more than 15 min at any occasion during 1 week)?

Yes	No
-----	----
- If the answer is yes, do you have to take special measures to empty the bowel?

(a) Strain for a long time/go to the toilet several times	
(b) Press with or by other means use the fingers to empty the bowel	
(c) Use a catheter	
6. Do you have difficulties with urination?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
7. (a) Can you differentiate between gas and faecal matter?

Yes	No
-----	----
- (b) Can you release gas without simultaneously having faecal leakage?

Yes	No
-----	----
- (c) Have you experienced episodes of leakage of gas (inability to voluntarily retain gas)?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
8. Have you experienced episodes of leakage of faecal matter in daytime?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
9. Have you experienced episodes of leakage of faecal matter during night?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/night	> Once/night
--------------	----------------------	------------------------	--------------
10. (a) Do you use a pad in the daytime against unexpected episodes of leakage?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
- (b) Do you use a pad during the night against unexpected episodes of leakage?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/night	> Once/night
--------------	----------------------	------------------------	--------------
11. Have you experienced episodes of leakage of urine?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
12. (a) Have you experienced episodes of abdominal pain?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
- (b) Have you experienced unpleasant cramping pain in relation to defaecation?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
- (c) Have you experienced episodes of anal pain?

Yes	No
-----	----
- If the answer is yes, how often?

< Once/month	Once/month–once/week	> Once/week–once/day	> Once/day
--------------	----------------------	----------------------	------------
13. Do you use any medication to regulate bowel function?

Yes	No
-----	----
- If yes, which type of preparations?

14. Do you use a diet to regulate bowel function?

Yes	No
-----	----
- If yes, which type of diet?

15. Do you visit the toilet

At regular intervals
When you feel a need to
16. Can you go to the city for shopping without knowing where the toilets are located?

Yes	No
-----	----
17. Has your bowel function influenced your working situation?

Yes	No
-----	----

If yes, in what way?		
18. Has your bowel function influenced your ability to go to parties, have guests?	Yes	No
If yes, in what way?		
19. Does your bowel function influence your choice of spare-time occupation, vacations?	Yes	No
If yes, in what way?		
20. (a) How would you characterize the outcome of the operation?	Excellent Good Acceptable Poor Extremely poor	
(b) If you had had knowledge about what you know today, would you then have had the same operation once again?	Yes	No
(c) Would you recommend a friend/relative with the same disease to have this operation?	Yes	No
(d) If you had known what you know today, would you then rather have had an ileostomy?	Yes	No
21. Other viewpoints, comments:		
Thank you for your participation!		

Raised levels of plasma Big Endothelin 1 in patients with colorectal cancer

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Background: The aim was to assess the role of plasma Big Endothelin (ET) 1 levels as a marker of disease presence and stage in colorectal adenocarcinoma.

Methods: Big ET-1 was measured in the plasma of 37 patients with colorectal cancer. Preoperative systemic plasma levels of Big ET-1 in patients with cancer were compared with levels in 20 age- and sex-matched controls. Portal plasma samples were collected at operation in addition to peripheral venous samples. Immunohistochemical staining for Big ET-1 was performed on a selection of primary tumour specimens and liver metastases.

Results: Median (range) preoperative systemic plasma levels of Big ET-1 were significantly higher in patients with cancer than in controls (1.0 (0.3–9.7) versus 0.2 (0.0–6.0) fmol/ml; $P=0.0001$). Intraoperative portal plasma levels of Big ET-1 were significantly higher in patients with Dukes' 'D' disease than in patients with Dukes' A, B and C disease (2.1 (1.4–10.0) versus 1.2 (0.3–6.6) fmol/ml; $P=0.01$). Similarly, systemic plasma levels were significantly higher in patients with Dukes' 'D' disease than in those with localized disease (1.9 (1.2–9.7) versus 1.2 (0.2–8.3) fmol/ml; $P=0.01$). The presence of microvascular invasion in the tumour specimens was associated with a significantly raised portal plasma level of Big ET-1 (1.6 (1.5–2.1) versus 1.1 (0.8–1.3) fmol/ml; $P=0.04$). Immunohistochemistry localized Big ET-1 to the cancer epithelial cells.

Conclusion: The plasma level of Big ET-1 is significantly raised in patients with colorectal cancer. Patients with liver metastases have significantly higher levels than those with localized disease.

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Introduction

The endothelins (ET) are a family of peptides with potent vasoactive properties¹. Three isoforms are recognized, ET-1, ET-2 and ET-3², the principal isoform in human plasma being ET-1³. In addition to their potent vasoconstrictor properties they are also believed to play a role in a diversity of other biological processes such as mitogenesis, regulation of DNA synthesis and stimulation of cell proliferation^{4–6}.

In vitro studies have demonstrated an increase in ET-1 production in a number of cancer cell lines, including mammary, pancreatic and colonic cell lines, and it is thought that the increased tissue levels have implications for tumour growth and cell proliferation^{7–9}. To date, only one *in vivo* study of ET-1 in colorectal cancer has been performed¹⁰. Raised levels were demonstrated in the plasma of patients with cancer compared with the control population but ET-1 measurement was not sufficiently sensitive to

differentiate between localized and metastatic disease. Immunohistochemical analysis of primary colorectal cancer tissues demonstrated ET-1 binding sites around both tumour cell nests and blood vessels.

Other studies have suggested alterations in the hepatic perfusion index (HPI) due to splanchnic vasoconstriction in metastatic disease¹¹. It may be postulated that ET-1 is involved in a dual paracrine role of enhanced tumour progression and splanchnic vasoconstriction in these patients.

Big ET-1, the biological precursor of ET-1, has a circulating half-life of 23 min¹² compared with only 3.5 min for ET-1¹³. Circulating ET-1 levels may grossly underestimate local tissue concentrations¹⁴, while Big ET-1 with its longer half-life has been implicated as a more sensitive indicator of endothelin system activation¹⁵.

The purpose of this study was to examine whether the Big ET-1 level was raised in the plasma of patients with colorectal cancer and to assess whether it may be used as an

indicator of disease severity. Portal and systemic plasma samples were collected to assess whether endothelin might account for the reported alterations in HPI associated with metastatic disease.

Patients and methods

From September 1998 to May 1999, a total of 37 patients with histologically proven colorectal adenocarcinoma were recruited prospectively into the study. All underwent laparotomy for the treatment of their disease. Twenty age- and sex-matched controls were recruited from a general surgical outpatient clinic. Before commencement, local ethics committee approval was obtained for the work contained in this study.

Blood from the control patients was collected from a peripheral arm vein. Preoperative systemic blood samples were collected at the time of admission for surgery in 14 of the 37 patients studied. Portal blood samples were obtained at operation by the operating surgeon from the principal portal tributary draining the tumour bed, just before ligation of the vessel. A systemic sample was collected simultaneously from a peripheral vein.

All blood samples were collected in ethylenediamine tetra-acetic acid (EDTA)-containing specimen tubes, placed immediately on to crushed ice and centrifuged within 15 min of collection. The plasma supernatant was drawn off, snap frozen in liquid nitrogen and stored at -80°C . All samples were assayed within 3 months of collection.

Measurement of plasma Big endothelin 1

EDTA plasma levels of Big ET-1 were measured using a one-step sandwich enzyme immunoassay kit (Biomedica, Divischgasse, Austria). Preliminary experiments using serial dilutions of representative plasma samples were used to determine the optimum sample dilution for the assay range. All standards and samples were assayed in duplicate and the mean value was taken. On completion of the assay, the observed colour change was read on a standard plate reader and plasma values were calculated by extrapolation from a standard curve. A separate standard curve was constructed for each immunoassay batch.

Immunohistochemistry

Immunohistochemical staining for Big ET-1 was performed on paraffin-embedded tissue samples 4 μm thick. A total of 28 tumour specimens were analysed, comprising four Dukes' stage A, seven Dukes' B, seven Dukes' C and ten

Dukes' 'D' tumours and their associated liver metastases. Sections of 'normal' liver were obtained from archival necropsy specimens within the department of pathology.

Primary antibodies were obtained commercially (Big ET-1: Peptides International, Louisville, Kentucky, USA; CD68 and CD3: Dako, Glostrup, Denmark). Briefly, sections were deparaffinized, rehydrated and then immersed in 6 per cent hydrogen peroxide for 10 min to quench endogenous peroxidase activity. Sections were preincubated with 5 per cent normal goat serum (NGS) in phosphate-buffered saline (PBS) for 30 min before incubation with the primary antibody for 18 h at 4°C . Both primary antibodies were prepared in 5 per cent NGS to minimize background staining. Immunostaining was performed using a commercially available avidin-biotin complex kit (Dako). After appropriate incubations with the secondary and tertiary antibodies, the sections were treated with diaminobenzidine for 5 min. They were exposed briefly to copper sulphate solution and then counterstained with haematoxylin. Negative controls were prepared by replacing the primary antibody with PBS.

Dukes staging

For the purposes of this study Dukes' A, B and C tumours were classified as localized tumours. Dukes' 'D' tumours were those with liver metastases irrespective of the stage of the primary lesion.

Statistical analysis

Values are expressed as median (range). Data did not follow a normal distribution. One-way analysis of variance was performed using the Kruskal-Wallis test. Mann-Whitney tests were used to analyse differences between data groups. Wilcoxon matched pairs test was used for paired data. The Spearman rank correlation test was used to determine association between variables.

Results

Patients

The 37 patients with cancer included 23 men and 14 women, of median (range) age 71 (40-90) years. There were 20 age- and sex-matched controls, 12 men and eight women aged 62 (40-85) years.

Preoperative plasma Big Endothelin 1 levels

The preoperative systemic plasma Big ET-1 level in patients with cancer was 1.0 (0.3-9.7) fmol/ml, a value

significantly higher than that in normal controls (0.2 (0.0–6.0) fmol/ml) ($P=0.0001$) (Fig. 1).

Intraoperative plasma Big Endothelin 1 levels

Systemic plasma levels were significantly higher in patients with Dukes' 'D' disease than in those with localized disease (Dukes' A, B and C): 1.9 (1.2–9.7) *versus* 1.2 (0.2–8.3) fmol/ml ($P=0.01$). Similarly, levels of Big ET-1 in portal blood from patients with Dukes' 'D' disease were significantly

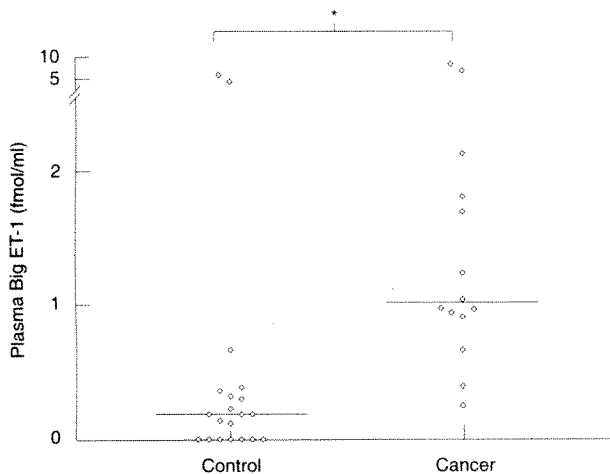


Fig. 1 Systemic levels of Big Endothelin (ET) 1 in controls ($n=20$) and preoperative samples from patients with cancer ($n=14$). Bars represent median values. * $P=0.0001$ (Mann-Whitney U test)

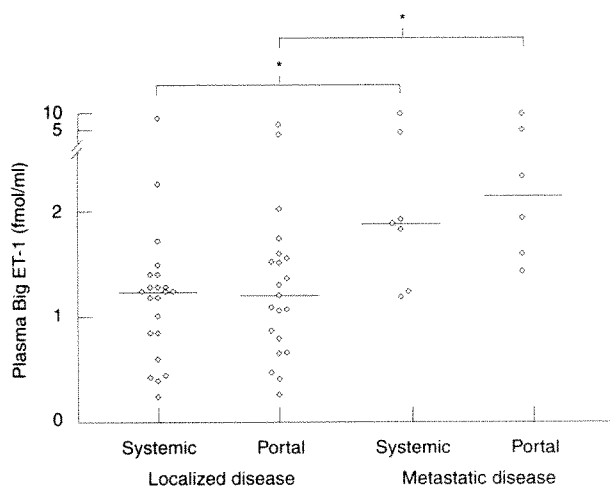


Fig. 2 Intraoperative plasma Big endothelin (ET) 1 levels in patients with localized (Dukes A, B and C) and metastatic (Dukes 'D') disease. Systemic and portal values are plotted separately for each group. Bars denote median values. * $P=0.01$ (Wilcoxon matched pairs). There was a significant correlation between systemic and portal values ($r_s=0.74$, $P<0.0001$, Spearman R)

raised compared with those in patients with localized disease: 2.1 (1.4–10.0) *versus* 1.2 (0.3–6.6) fmol/ml ($P=0.01$) (Fig. 2). There was no significant difference between portal and systemic plasma levels of Big ET-1 ($r_s=0.74$, $P<0.0001$).

There was no significant difference in plasma Big ET-1 levels between patients with rectal tumours and those with colonic tumours: 1.2 (0.2–9.7) *versus* 1.2 (0.3–4.3) fmol/ml ($P=0.60$). Similarly, no significant correlation existed between tumour size and plasma Big ET-1 level ($r_s=0.09$, $P=0.60$).

The presence of vascular invasion in the tumour specimen was associated with a significant increase in portal Big ET-1 level: 1.6 (1.5–2.1) *versus* 1.1 (0.8–1.3) fmol/ml ($P=0.04$).

Immunohistochemistry

In primary tumour tissues, staining for Big ET-1 was positive in the epithelial cancer cells in all but three of the tumours studied (one Dukes' B, two Dukes' C). Viewing sections at high magnification suggested a cytoplasmic origin for the increased immunoreactivity. Positive staining was also observed in scattered cells throughout the tumour stroma. In serial sections these cells were positive for CD68, confirming their identity as macrophages. In contrast, staining for Big ET-1 was found to be negative in adjacent normal colorectal epithelium in all but one of the ten cases examined (Fig. 3).

Metastatic cancer cells present in the liver also stained positively for Big ET-1. Normal hepatocytes in livers containing tumour also appeared to stain more intensely for Big ET-1 than hepatocytes in control livers taken from necropsy specimens.

Discussion

A significant proportion of patients who undergo potentially curative resection for carcinoma of the bowel will subsequently succumb to metastatic disease of the liver¹⁶. Early identification and selection of such patients for adjuvant therapy is required if their prognosis is to be improved. Shankar *et al.*¹⁰ found raised levels of ET-1 in the plasma of patients with colorectal cancer, but ET-1 measurement was not sufficiently sensitive to allow differentiation between patients with localized and metastatic disease. In this study measurement of Big ET-1, the biological precursor of ET-1, was performed, as previous work has suggested that it may be a more accurate indicator of the degree of activation of the endothelin system^{15,17}.

Levels of Big ET-1 in preoperative systemic plasma samples were found to be significantly higher in patients

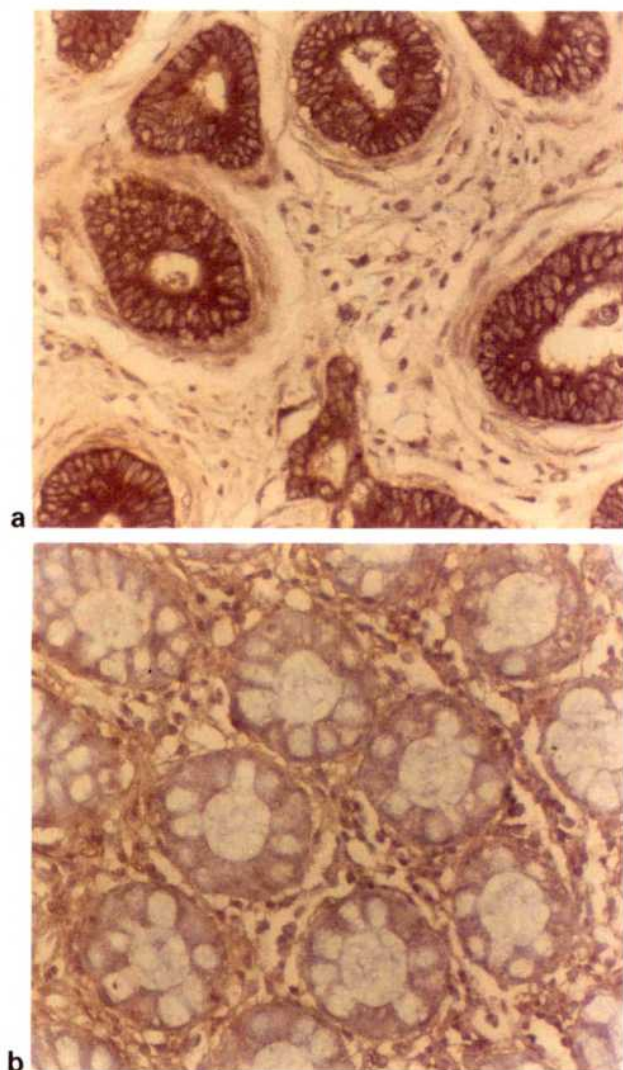


Fig. 3 (a) Positive staining for big ET-1 in colorectal cancer epithelium with (b) negative staining in adjacent normal colonic epithelium

with cancer than in age- and sex-matched controls. Patients with liver metastases were found to have significantly raised plasma levels of Big ET-1 in both portal and systemic samples compared with levels in patients with localized disease. Levels in patients with Dukes' A, B and C tumours were not significantly different, suggesting a particular association with the presence of liver metastases. There was no significant correlation between Big ET-1 and the size of the primary tumour. These findings suggest that it is the presence of tumour in the liver that causes an increase in plasma Big ET-1 concentration.

It is of interest to note that the level of Big ET-1 was significantly raised in patients with histopathological evidence of portal venous invasion. This may simply reflect release of Big ET-1-containing cancer epithelial cells into

the portal circulation. However, it may also be noted that a number of patients with localized disease had disproportionately high plasma Big ET-1 levels (Fig. 2). Patient follow-up will reveal whether those with high Big ET-1 plasma levels, but apparently localized disease, represent a subset of patients with widespread micrometastatic disease at the time of surgery.

Animal and human studies have demonstrated an increase in HPI (i.e. the relative hepatic arterial contribution to total liver blood flow) in the presence of liver metastases^{11,17-19}. It has been suggested that changes in HPI in the presence of liver metastases are due primarily to a decrease in portal venous flow^{11,17}. This has been attributed to a humoral mediator causing portal vasoconstriction, rather than obstruction by tumour tissues^{11,20}.

There was no significant difference between portal and systemic plasma levels in either localized or metastatic disease, suggesting steady-state levels of the enzyme in both circulations. De Nucci *et al.*¹⁴ have shown that the vasoconstrictor properties of ET-1 are more potent on venous as opposed to arterial smooth muscle. It is possible that a general increase in circulating endothelins at levels associated with metastatic disease could potentiate portal vasoconstriction to excess, but further work is necessary to substantiate whether Big ET-1 or its metabolites are responsible for the alterations in HPI.

In this study cytoplasmic staining for Big ET-1 was demonstrated in colorectal cancer epithelial cells *in vivo* in all but three of the cases studied. With the exception of one case, no such staining was apparent in normal colorectal epithelium. Shankar *et al.*¹⁰ demonstrated staining for ET-1 in the cytoplasm of tumour cells in colorectal liver metastases. Others have implicated endothelin involvement in the promotion of DNA synthesis, mitogenesis, angiogenesis, cell proliferation and cellular hypertrophy⁴⁻⁶. Thus the pathological significance of the increased expression of these endothelins may well lie outside their commonly accepted role as vasoconstrictors. Indeed, in the neoplastic context, their role as growth promoters might be more important.

Of particular interest was the observation that surrounding 'normal' hepatocytes appeared to stain more intensely for Big ET-1 in livers containing tumour than in control specimens. Further quantitative studies are required to verify this observation and are ongoing in this laboratory. If proven, this might in itself account for the raised levels of circulating Big ET-1 seen in Dukes' 'D' disease.

In summary, these results suggest that endothelins play a role in colorectal tumour genesis *in vivo*. Significantly raised levels of Big ET-1 have been demonstrated in the plasma of patients with colorectal cancer and the principal source of this increased production has been

localized to epithelial cancer cells. Venous blood levels in patients with liver metastases were significantly higher than in those with localized disease, supporting the hypothesis that Big ET-1 is a more sensitive indicator of endothelin activation than measurement of ET-1 and raising questions as to the pathological significance of such findings.

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Clinical presentation of the pseudomyxoma peritonei syndrome

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Background: Pseudomyxoma peritonei syndrome is characterized by a gradual expansion of mucoid tumour and fluid at specific sites within abdominopelvic regions as a result of a perforated appendiceal adenoma. The aim was to analyse the presenting symptoms and signs of patients with this condition.

Methods: Of 410 patients with appendiceal tumours 217 had the diagnosis of pseudomyxoma peritonei syndrome with histological confirmation. A retrospective review of the clinical characteristics that determine presentation was performed.

Results: Overall, suspected acute appendicitis was the most common presentation (27 per cent). For women the diagnosis was most commonly made while being evaluated for an ovarian mass (39 per cent). Increasing abdominal girth was the second most common presentation overall (23 per cent). Thirty patients (14 per cent) presented with new-onset hernia, of which the majority (26) were inguinal hernias.

Conclusion: Consideration of appendicitis, increased abdominal girth, ovarian mass and new-onset hernia as caused by this syndrome may facilitate diagnosis and definitive treatment.

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Introduction

Pseudomyxoma peritonei represents a slowly progressive disease process characterized by copious amounts of mucoid fluid and tumour that, over time, fills the peritoneal cavity. Literally defined, it means 'false mucinous tumour of the peritoneum'¹. Early descriptions of this condition identified an appendiceal mucinous tumour as the primary site of disease². However, a lack of knowledge concerning the pathogenesis of this rare condition caused numerous diseases that result in extensive mucus accumulation within the abdomen and pelvis to be called pseudomyxoma peritonei. This occurred when the tumour originated from a mucinous adenoma of the appendix, a mucus-producing gastrointestinal adenocarcinoma, a primary ovarian mucinous tumour, or mucinous peritoneal carcinomatosis of an unknown primary tumour.

Sugarbaker and colleagues³ attempted to redefine a clinical entity which they called the pseudomyxoma peritonei syndrome. They proposed that the term pseudomyxoma peritonei syndrome should be strictly limited to identify a pathologically and prognostically homogeneous group of patients characterized by histologically benign peritoneal tumours associated with a primary appendiceal

mucinous adenoma. This tumour has an indolent clinical course and is not considered biologically aggressive because it does not invade or metastasize. Pathologically the peritoneal mucinous lesions are termed 'disseminated peritoneal adenomucinosis' or simply 'adenomucinosis'⁴. According to this definition, cases of mucinous peritoneal carcinomatosis from primary sites other than the appendix, regardless of the presence of abundant extracellular mucin, should not be included as pseudomyxoma peritonei syndrome.

In the past treatment consisted of repeated operative procedures focused at evacuating as much mucinous tumour and free mucus as possible. Eventually there were no further surgical options and the patients succumbed to intestinal obstruction and terminal starvation. This approach resulted in a median survival of 2.5 years, with few patients being alive after 5 years^{5–7}. Currently, peritonectomy procedures that allow the surgeon to remove completely all involved parietal and visceral peritoneum, combined with techniques to deliver perioperative intraperitoneal chemotherapy, have changed the approach to the patient with pseudomyxoma peritonei syndrome^{8,9}. No longer is the therapy focused on palliation with surgical procedures that temporarily relieve symptoms, but has

Table 1 Clinical presentation of 217 patients with pseudomyxoma peritonei syndrome

	No. of patients	Men	Women
Appendicitis	58 (27)	36 (34)	22 (20)
Increased abdominal girth	49 (23)	28 (27)	21 (19)
Ovarian mass	44 (20)	—	44 (39)
Hernia	30 (14)	26 (25)	4 (4)
Ascites	9 (4)	5 (5)	4 (4)
Abdominal pain	8 (4)	5 (5)	3 (3)
Other	19 (9)	5 (5)	14 (12)
Total	217 (100)	105 (48)	112 (52)

Values in parentheses are percentages

curative intent. The outcome of these patients is now an 87 per cent 5-year disease-free survival rate⁶.

The purpose of this study was to analyse the presenting symptoms of all the patients with the pseudomyxoma peritonei syndrome treated by a single surgeon (P.H.S.) over a 13-year period. An analysis of their clinical presentation will further characterize the syndrome and assist the clinician in the identification of patients for curative treatments without unnecessary delay.

Patients and methods

The research records of all the patients with primary appendiceal tumours treated by a single surgeon from February 1985 to October 1998 were reviewed. There were 410 patients with appendiceal malignancy. Of these, 217 patients had the diagnosis of pseudomyxoma peritonei syndrome with a histological confirmation of 'disseminated peritoneal adenomucinosis' resulting from an appendiceal adenoma. Patients who had hybrid appendiceal malignancy were not included; the hybrid tumours were composed largely of adenomucinosis but had components of mucinous adenocarcinoma identified by histological examination⁴. Patients with mucinous adenocarcinomas of the appendix were not included⁴. An analysis of these 217 patients constitutes the basis of the study.

The patients were classified into one of seven groups based on their clinical presentation. Group 1 included patients in whom the diagnosis of pseudomyxoma peritonei syndrome was made at the time they underwent surgery for suspected appendicitis. Group 2 included patients whose initial medical evaluation was performed because of increasing abdominal girth. In this group the patients or family member initially called attention to the expanding abdomen. Group 3 included women whose original presentation was for an ovarian mass. Group 4 included those in whom mucoid material was found during hernia

repair. These patients did not have symptoms other than a new-onset hernia. Group 5 included those who presented with non-specific complaints and an outside physician gave a diagnosis of ascites. Investigation for this condition led to the diagnosis of pseudomyxoma peritonei syndrome. Patients with an increasing abdominal girth (a symptom) were sufficiently different from those presenting with ascites (a sign) to constitute separate groups. In one group the patient complained of an expanding abdomen. In the group with ascites a physician's examination or radiological test was necessary to identify fluid within the peritoneal cavity. Group 6 included patients who presented with a chief complaint of abdominal pain. Group 7 represented all the patients who were not included in any of the above groups. None of these patients had additional symptoms that were obviously related to pseudomyxoma peritonei syndrome.

The treatment strategy uniformly involved two principles of management in these patients. First, peritonectomy procedures were used in an attempt to achieve a disease-free status. These procedures involved greater and lesser omentectomy, stripping of the right and left hemidiaphragm, stripping of the pelvis and visceral resections that were required in order to eliminate macroscopic disease surgically. Normal peritoneal surfaces were not stripped away⁹. After operation the peritoneal space was treated with mitomycin C at 12.5 mg/m² for men and 10 mg/m² in women. The chemotherapy was instilled in a large volume of 1.5 per cent dextrose peritoneal dialysis solution in order to promote uniform distribution of the drug to all peritoneal surfaces. Mitomycin C treatment was followed by 5 days of intraperitoneal 5-fluorouracil chemotherapy instilled directly into the abdomen in 1 litre of 1.5 per cent dextrose peritoneal dialysis solution. Other treatments such as additional cycles of combined intraperitoneal and systemic chemotherapy, intravenous continuous infusion of 5-fluorouracil and intravenous irinotecan were used after referral back to the local physician on a sporadic basis.

Results

There were 217 patients with the diagnosis of pseudomyxoma peritonei syndrome of appendiceal origin (Table 1). Analysis of the distribution by sex showed no sex preference, with 112 (52 per cent) of the patients being women and 105 (48 per cent) men. The age range was 29–76 (median 49) years.

Suspected acute appendicitis was the most common form of presentation overall, with 58 (27 per cent) of the 217 patients presenting in this manner. When analysed by sex, it constituted the most common presentation for men, with 36

Table 2 Anatomical distribution of 30 hernias in 217 patients with pseudomyxoma peritonei syndrome

	No. of patients	Inguinal		Total	Umbilical
		Right	Left		
Men	26	10	9	19	7
Women	4	1	—	1	3
Total	30	11	9	20	10

men (34 per cent) being diagnosed with pseudomyxoma peritonei syndrome at the time of exploration for acute appendicitis. It constituted the second most common presentation in women, with 22 patients (20 per cent).

Increasing abdominal girth, not associated with any other signs or symptoms, was the second most common presentation overall, with 49 patients (23 per cent) seeking medical evaluation because of an expanding abdomen. When analysed by sex, it was the second most common presentation for men (27 per cent) and the third most common presentation for women (19 per cent).

For women the diagnosis most commonly resulted from the evaluation of an ovarian mass. Forty-four women (39 per cent) presented in this way. These patients had pelvic symptoms. On pelvic examination or ultrasonography as part of the investigation of these patients, an ovarian mass secondary to the perforated appendiceal adenoma was discovered.

Presentation with a new-onset hernia was the fourth most common clinical entity, recorded in 30 (14 per cent). Twenty hernias were inguinal and the other ten umbilical. The majority of the hernias (26 of 30) were present in men (Table 2).

Nine patients (4 per cent) had the diagnosis of pseudomyxoma peritonei syndrome established when ascites was diagnosed by a radiological test and subsequently sampled by paracentesis. This represents a small group of both men and women. In almost all patients the intra-abdominal fluid accumulation is usually a thick mucoid material. In these nine patients it was a thin serous fluid.

Eight patients (4 per cent) presented with vague non-specific abdominal pain. Investigation for this pain, usually with computed tomography of the abdomen and pelvis, led to the diagnosis of pseudomyxoma peritonei syndrome.

Nineteen of the 217 patients were grouped in the 'other' category. Five of these were men and 14 women. There was a wide variety of initial signs and symptoms, some of which were incidental findings. In women, the majority were associated with gynaecological complaints or investigation for infertility (Table 3).

Table 3 Less common initial presentation in 19 of 217 patients with pseudomyxoma peritonei syndrome

	No. of patients
Women	
Infertility investigation	3
Presumed cholecystitis	3
Postmenopausal bleeding	2
Abnormal Papanicolaou smear	1
Pelvic pain	1
Pelvic mass	1
Surgery for fibroids	1
Laparoscopy for tubal ligation	1
Surgery for right colonic cancer	1
Total	14
Men	
Abdominal aortic aneurysm repair	1
Deep vein thrombosis	1
Rectal bleeding	1
Nephrectomy	1
Anaemia	1
Total	5

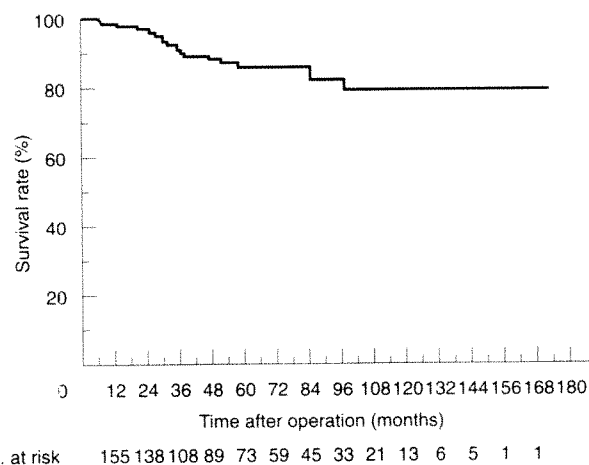


Fig. 1 Kaplan-Meier survival distribution of patients with the pseudomyxoma peritonei syndrome treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy. Some 217 patients were evaluated at the Washington Hospital Center. Follow-up data are available for 168 patients who had treatment at this institution (three patients lost to follow-up)

The median follow-up of the 168 patients treated at this institution is 46.7 months. The median survival has not yet occurred. The 5-year survival predicted by a Kaplan-Meier distribution is 81 per cent. Fig. 1 shows the survival distribution for these patients.

The mortality rate for these 168 patients was 3 per cent in-hospital or within 3 months of operation. Survival, morbidity and mortality were not significantly related to the presenting symptom or sign.

Discussion

Current thinking regarding the pathophysiology of the pseudomyxoma peritonei syndrome can be summarized as follows. An adenoma arises within the appendiceal lumen and with progressive growth the lumen of the appendix becomes occluded. This occlusion leads to distension of the distal portion of the appendix, not only by mucus produced by the normal appendiceal epithelium but also by the adenoma. The wall of the appendix ruptures and leak of mucus containing epithelial cells from the adenoma occurs³.

Analysis of the present data indicates that this process is, in a majority of patients, a subclinical event. Even the patients diagnosed with pseudomyxoma peritonei syndrome while undergoing an operation for suspected acute appendicitis already had significant disease present throughout the abdomen and pelvis. The most likely explanation is that the appendix may repeatedly decompress by perforation and resealing. The primary lesion grows little in size over the years but the epithelial cells, widely distributed around the peritoneal space, continue to proliferate and produce large quantities of mucus. Eventually an episode of appendiceal distension and rupture will result in bacterial contamination and the symptoms of appendicitis may occur. In many of the patients who were operated on for acute appendicitis, it was reported that mucus was extruding from the lumen of the appendix into the peritoneal cavity. In the present study, symptoms of appendicitis occurred in 58 (27 per cent) of the 217 patients and was the most common presentation.

The location and quantity of mucinous tumour within the abdomen and pelvis can be characterized by the redistribution phenomenon³. Tumour cells are surrounded by a slippery mucoid matrix and move with the normal flow of the peritoneal fluid. Portions of the peritoneum that are in motion, such as the visceral peritoneum on the small bowel surface, are seeded only sparsely. The abdominal surfaces that absorb peritoneal fluid, such as the greater omentum and the undersurface of the diaphragm, are coated by tumour cells as fluid is pulled to these anatomical sites. Massive accumulation of tumour in the greater omentum contributes significantly to the increase in the patients' abdominal girth, which was the second most common clinical presentation, occurring in 23 per cent of patients.

In 39 per cent of women the clinical presentation was that of an ovarian mass. The pathophysiology of an ovarian mass occurring in the presence of a perforated appendiceal adenoma can be understood by studying the ovarian physiology during ovulation. The reproductive system of the female shows regular cyclical changes. At the follicular

phase of each ovarian cycle one ovarian follicle starts to grow and distend. At about the day 14 of the menstrual cycle the distended follicle ruptures and the ovum is extruded into the abdomen. The follicle that ruptured promptly fills with blood forming a corpus haemorrhagicum. At the time of the ovarian follicle rupture, epithelial cells floating freely in peritoneal fluid adhere to the ruptured follicle. These tumour cells become trapped in the corpus luteum and proliferate inside the ovary while the surface of the ovary undergoes its natural cicatricial process with no evidence of the mucinous tumour within. Over time a cystic ovarian mass caused by an expansion of mucinous tumour cells will become symptomatic or detectable by pelvic examination. This symptom was not recorded in postmenopausal women.

The free-floating tumour cells that migrate with the peritoneal fluid around the abdomen and pelvis may accumulate in an umbilical hernia sac or a patent processus vaginalis. As these tumour cells proliferate and continued mucus production occurs, they may produce a new-onset umbilical or inguinal hernia. Hernia was the fourth most common presentation in this series.

The treatment strategy used in this series resulted in an 81 per cent 5-year survival rate. There was a 3 per cent mortality rate associated with the treatments⁷. Prompt recognition of the clinical presentation of pseudomyxoma peritonei syndrome combined with aggressive treatments using peritonectomy and perioperative intraperitoneal chemotherapy resulted in a beneficial result. As earlier referrals occur, the survival statistic is likely to improve and the morbidity and mortality rates reduce.

In summary, the pseudomyxoma peritonei syndrome is caused by an appendiceal adenoma that distends the appendix and ruptures, releasing mucus-producing tumour cells into the peritoneal cavity. In most patients the initial appendiceal perforation is a subclinical event. Mucinous tumour progression and mucus production continue, redistributing the process throughout the abdomen and pelvis. The site at which the process causes a presenting sign or symptom is dictated by patient factors such as the progression within a hernia sac or in a ruptured ovarian follicle. Cytoreductive surgery using peritonectomy combined with perioperative intraperitoneal chemotherapy was employed successfully as a potentially curative treatment strategy in these patients.

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Recurrent sigmoid volvulus treated by percutaneous endoscopic colostomy

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Introduction

Sigmoid volvulus is a life-threatening condition which often occurs in elderly patients with physical and mental illness. If the sigmoid colon is ischaemic, emergency resection is the only treatment option and is associated with a mortality rate of up to 33 per cent¹. Otherwise, conventional treatment is endoscopic decompression, but the recurrence rate is over 40 per cent². Elective open or laparoscopic fixation or resection may be inappropriate or unsafe in frail and elderly patients. Percutaneous endoscopic colostomy may provide a safe and effective treatment option in recurrent sigmoid volvulus in selected patients³. The Academy of Medical Royal Colleges for SERNIP (Safety and Efficacy Register of New Interventional Procedures) has approved the technique as category C. This paper provides details of the technique, complications and results.

Patients and methods

Fourteen patients aged 53–99 (mean 78) years with recurrent sigmoid volvulus in whom conventional surgery was considered to be unsafe or inappropriate were treated by percutaneous endoscopic colostomy after reduction of the acute volvulus endoscopically.

Following standard bowel preparation and intravenous administration of cefuroxime 750 mg, metronidazole 500 mg and midazolam (Hypnovel; Roche, Welwyn Garden City, UK), a colonoscope is passed into the proximal sigmoid colon. With good transillumination a 14-Ch gastrostomy tube (Freka, Frenius, Warrington, UK) is placed under local anaesthesia using a standard percutaneous gastrostomy technique. The procedure is repeated in

the distal sigmoid colon, bringing the second tube through the abdominal wall as far from the first as possible to anchor the sigmoid colon to the anterior abdominal wall in two places. Patients may eat and drink immediately and are discharged as soon as domestic circumstances allow, with an information leaflet on care of the tubes for the patient or carer.

In the first eight patients the colostomy tubes were removed at 6 weeks but volvulus recurred in three patients. Subsequent tubes have been changed for flat Mic-Key tubes (Vygon, Cirencester, UK) which have been left *in situ* indefinitely.

Results and discussion

There were no deaths associated with the procedure or from sigmoid volvulus. Three patients died at 6–24 months from other causes. Volvulus recurred in three of eight patients after early removal of the colostomy tubes. Laparotomy in these patients showed no residual fixation of the colon. One patient with learning difficulties inadvertently pulled out the colostomy tube within 24 h and therefore underwent sigmoid resection. In five patients whose tubes have been left *in situ*, no recurrence has occurred after follow-up of 7–21 (mean 12.6) months. There were no septic or other complications.

These results show that percutaneous endoscopic colostomy, under intravenous sedation and local anaesthesia, is a safe and effective treatment for recurrent sigmoid volvulus, particularly in patients in whom conventional surgery is considered unsafe or inappropriate. Early removal of the tubes resulted in recurrent volvulus in three of eight patients owing to failure of the colon to adhere to the anterior abdominal wall. No recurrence has occurred in patients in whom tubes have been left *in situ*. The Mic-Key tubes, with a flat external flange, have caused no problems, have proven acceptable to patients and carers, and have been easily changed when necessary.

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Effect of surgical subspecialization on breast cancer outcome

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Background: There is increasing pressure for specialization of medical services. The effect of surgical specialization on the outcome of breast cancer in Bedford has been assessed.

Methods: The Bedford Breast Cancer Registry, which contains prospective diagnostic, treatment and follow-up data on all breast cancers treated in North Bedfordshire, was analysed to compare breast cancer outcome between 1990–1992 and 1993–1996, that is before and after the advent of surgical subspecialization. All 784 patients were analysed, including patients with metastases (4 per cent) and those treated by tamoxifen alone (8 per cent). Outcome was compared in terms of disease-free survival (DFS), locoregional and all (locoregional and metastases) recurrence rates assessed by Cox proportional hazard and Kaplan–Meier analyses.

Results: Overall DFS was 75 per cent and the locoregional recurrence rate was 8 per cent at 3 years. The tumour stage and grade at presentation and the proportion of screen-detected cancers were similar for both intervals. The outcome for patients before specialization (1990–1992; $n = 329$) was worse: hazard ratio (HR) for DFS 1.5 (95 per cent confidence interval 1.2–2.0) and HR for locoregional recurrence 2.0 (1.2–3.5). After subspecialization (1993–1996, $n = 455$) DFS improved from 70 to 79 per cent ($P = 0.009$) and the all recurrence rate fell from 22 to 12 per cent ($P = 0.0004$) at 3 years. The improvement in outcome was mainly in younger patients (aged less than 70 years), in whom DFS improved from 72 to 81 per cent ($P = 0.02$) and the all recurrence rate fell from 24 to 12 per cent ($P = 0.001$) at 3 years. The improvement was associated with increased axillary surgery (47 to 74 per cent; $P < 0.0001$), and more frequent use of tamoxifen (74 to 84 per cent; $P = 0.004$) and chemotherapy (10 to 27 per cent; $P < 0.0001$) in this age group.

Conclusion: There was a significant improvement in outcome for patients with breast cancer after surgical subspecialization in Bedford. This may relate to the more frequent use of appropriate systemic therapy.

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Introduction

Many reports have established the outcome and prognostic indicators for breast cancer^{1–4}. However, these publications are often specific studies on selected patients with small cancers^{1,2} or rely on less detailed National Registry data^{3,4}. There is a dearth of complete data sets that include all breast cancers seen in a defined geographical area over a long interval including both the National Health Service and private sectors, with full prospective documentation of diagnosis, treatment and follow-up. The Bedford Breast Cancer Registry (BBCR) contains this information on all breast cancers diagnosed and treated in North Bedfordshire, a population of 260 000 served by a single district general hospital.

The National Registry data have been used to make unfavourable comparisons between breast cancer survival in Britain and other developed countries, which led in part to the Calman report⁵ into the provision of all cancer care in the UK and the Haward report⁶ into breast cancer care. Both reports recommended increasing surgical specialization and the development of specialist cancer units in district general hospitals. Although it is a reasonable assumption that these changes will improve survival, evidence to support this assumption is scarce.

The BBCR database contains all patients with breast cancer diagnosed in North Bedfordshire since the beginning of 1990, including those with advanced or disseminated disease, patients treated in the private sector and patients not receiving surgical intervention. The patients

Table 1 Comparison of characteristics in patients with breast cancer, 1990–1992 and 1993–1996

	1990–1992 (n=329)	1993–1996 (n=455)	P*
Age (years)			0.4
<50	76 (23)	104 (23)	
50–69	163 (50)	189 (41)	
≥70	90 (27)	162 (36)	
Screening referrals	46 (14)	68 (15)	0.6
Tumour stage			0.28
<i>In situ</i>	10 (3)	27 (6)	
T ₁	168 (51)	225 (49)	
T ₂	99 (30)	130 (29)	
T ₃	14 (4)	20 (4)	
T ₄	38 (12)	53 (12)	
Axillary node status			0.55
Node positive	96 (29)	124 (27)	
Node negative	233 (71)	331 (73)	
Metastases	17 (5)	15 (3)	0.4
Grade			0.12
Well differentiated	59 (18)	77 (17)	
Moderately differentiated	102 (31)	155 (34)	
Poorly differentiated	133 (40)	154 (34)	
Grade unknown	35 (11)	69 (15)	

Values in parentheses are percentages. * χ^2 test

were managed by all five local surgeons until the beginning of 1993. At this point a decision was taken to concentrate the diagnosis and treatment of all breast disease in the hands of two consultant surgeons. Arrangements for oncological, radiological and pathological services were not significantly changed until after 1996, with the development of the oncology unit on site and specialization of the radiological service. This study analysed the results for patients diagnosed with breast cancer between 1990 and 1996, and assessed the determinants of successful outcome, in particular the effect of surgical subspecialization.

Patients and methods

Patient identification

All patients with breast cancer were identified at the time of diagnosis by the clinician or breast care nurse and added to the register. Cross checks were carried out at 6-month intervals with the pathology, cytology and radiology computer systems to ensure that all patients were included.

Patients' case notes were flagged at the time of registration with a special BCCR sticker. A copy of all subsequent correspondence was sent to the BCCR office to aid follow-up.

Surgical subspecialization

From 1990 to the end of 1992 patients with breast cancer were referred to one of five consultant surgeons (ten to 38 new patients per year). From the start of 1993 new breast cancers have been assessed by one of two consultants (65–75 new patients per year). A consultant was involved with the outpatient assessment of the majority of new patients with breast cancer.

Data collection and analysis

Patients' characteristics, diagnostic details, tumour stage (tumour node metastasis (TNM) pathological classification or clinical classification for those not undergoing surgery) and treatment modalities were collected at the time of diagnosis. Follow-up information was added subsequently. For patients treated by tamoxifen alone, local recurrence was defined as progressive increase in the tumour on two subsequent follow-up visits, when further intervention was considered. For patients with metastases at presentation, distant recurrence was defined as evidence of further metastases at a different site. A customized application using a database (Dbase IV, Borland, Scotts Valley, CA, USA) was used for data entry and manipulation of data subsets. These subsets were subsequently transferred to a spreadsheet (Excel; Microsoft Corporation, Redmond, Washington, USA) and statistical package (Statview 6.0, Abacus Concepts, Berkeley, CA, USA) for analysis. Cox proportional regression analysis and Kaplan–Meier survival analysis were used to assess prognostic factors determining disease-free survival (DFS) and recurrence. The influence of surgical subspecialization was investigated by comparing outcomes for patients diagnosed between January 1990 and December 1992 with that of patients diagnosed between January 1993 and December 1996. Univariate comparisons were performed using χ^2 test, analysis of variance and *t* test, while survival analyses were compared by the log rank test.

Results

Overall outcome

A total of 784 patients with breast cancer were treated, of median age 62 (range 27–97) years. Median follow-up was 45 (range 18–60) months. Early stage tumours were more common (5 per cent *in situ*, 50 per cent T₁, 29 per cent T₂, 4 per cent T₃ and 12 per cent T₄). There were 72 per cent axillary node-negative and 28 per cent node-positive tumours (Table 1). Thirty-two patients (4 per cent) were found to have metastases at presentation. Most patients required breast surgery (wide local excision 55 per cent, mastectomy 37 per cent); only 8 per cent of patients were

Table 2 Comparison of treatment of patients with breast cancer, 1990–1992 and 1993–1996

	1990–1992 (<i>n</i> = 329)	1993–1996 (<i>n</i> = 455)	<i>P</i> *
Wide local excision	181 (55)	246 (54)	0.31
Mastectomy	125 (38)	164 (36)	0.5
Axillary dissection	135 (41)	282 (62)	<0.0001
Tamoxifen	263 (80)	401 (88)	0.002
Radiotherapy to breast	174 (53)	269 (59)	0.1
Radiotherapy to axilla	125 (38)	137 (30)	0.04
Chemotherapy	23 (7)	82 (18)	<0.0001

Values in parentheses are percentages. * χ^2 test

treated by tamoxifen alone (*Table 2*). DFS was 89 per cent at 1 year and 75 per cent at 3 years, while the locoregional recurrence rate was 3 per cent at 1 year and 8 per cent at 3 years. Outcome was similar for patients treated by wide local excision or mastectomy: DFS 78 and 75 per cent respectively at 3 years ($P = 0.5$).

Effect of stage, grade and age

Cox proportional regression analysis identified two principal determinants of outcome for DFS and recurrence. These were tumour grade and nodal status. For poorly differentiated tumours the hazard ratio (HR) for DFS was 2.8 (95 per cent confidence interval 1.6–4.7) and for local recurrence the HR was 6.8 (2.6–17.9). For node-negative patients the HR for DFS was 0.5 (0.4–0.7) and that for local recurrence was 0.3 (0.2–0.6). T stage did not add independently to these factors (HR for T₁ tumours: DFS 0.5 (0.2–1.2) and recurrence 0.3 (0.1–1.0)); both node status and tumour grade were related to T stage. Using tumour grade and lymph node status it was possible to divide patients into three prognostic groups. Patients with a well or moderately differentiated tumour and negative axillary nodes had the best outcome: DFS was 94 per cent at 1 year and 86 per cent at 3 years. Patients with a poorly differentiated tumour and negative nodes had an intermediate outcome: DFS 93 per cent at 1 year and 73 per cent at 3 years. Patients who were lymph node positive with a moderately or poorly differentiated tumour had an unfavourable prognosis: DFS 73 per cent at 1 year and 50 per cent at 3 years.

Outcome for screen-detected cancers

Fifteen per cent of the 784 patients were referred from the Breast Screening Programme. The tumour stage and grade were more favourable in this group. Screen-

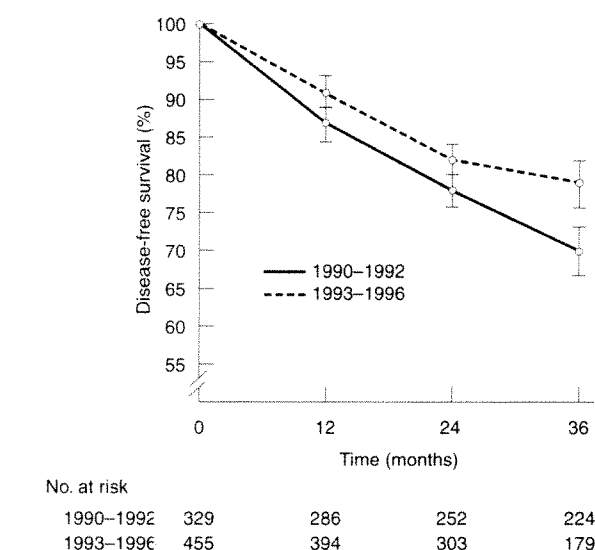


Fig. 1 Comparison of disease-free survival for patients treated in the intervals 1990–1992 and 1993–1996. Outcome was significantly better for patients treated between 1993 and 1996 ($P = 0.009$, log rank test). Standard error shown

detected tumours were more frequently suitable for treatment by wide local excision and rarely required chemotherapy. The outcome for this group of patients was very favourable. The DFS was 97 per cent at 1 year and 94 per cent at 3 years, compared with 88 and 71 per cent respectively for patients with breast cancer detected clinically ($P < 0.0001$). The recurrence rate (locoregional and metastases) was 2 per cent at 1 year and 5 per cent at 3 years for screened patients, compared with 7 and 19 per cent respectively for cancers detected clinically ($P = 0.0002$).

Outcome after surgical subspecialization

Patients with breast cancer diagnosed since 1993 ($n = 455$) were compared with those presenting from 1990 to the end of 1992 ($n = 329$). Patients treated since 1993 had a significantly improved outcome. DFS improved from 87 and 70 per cent to 91 and 79 per cent at 1 and 3 years respectively ($P = 0.009$; HR for 1990–1992 was 1.5 (1.2–2.0)) (*Fig. 1*). This was principally the result of a decrease in recurrences. The all recurrence rate (metastases and locoregional relapse) decreased from 22 to 12 per cent at 3 years ($P = 0.0004$; HR for 1990–1992 was 2.0 (1.2–3.5)) (*Fig. 2*). Tumour stage, grade and proportion of screen-detected cancers were similar for these two intervals, as was the type of surgical treatment to the breast (*Tables 1 and 2*).

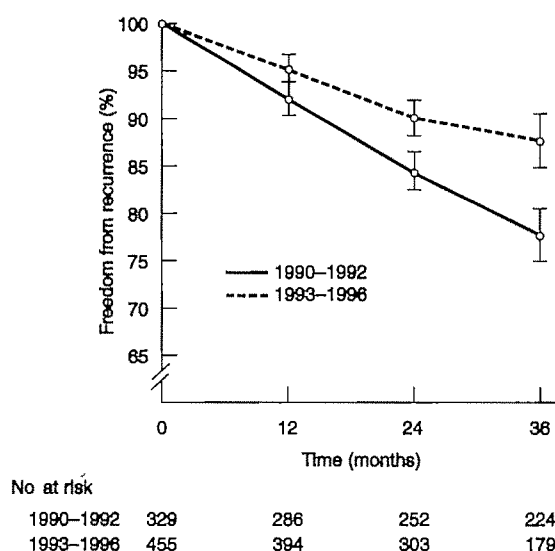


Fig. 2 Comparison of recurrence rates for patients treated in the intervals 1990-1992 and 1993-1996. Outcome was significantly better for patients treated between 1993 and 1996 ($P=0.0004$, log rank test). Standard error shown

However, more patients underwent axillary dissection and were treated with tamoxifen or chemotherapy in the second time interval (Table 2).

The improvement in outcome was evident for both favourable and poor stage/grade tumours. For favourable tumours the all recurrence rate fell from 17 to 9 per cent ($P<0.001$) while for unfavourable tumours (moderately or poorly differentiated and lymph node positive) the recurrence rate fell from 48 to 30 per cent at 3 years ($P<0.001$). The improvement in outcome was principally in patients under 70 years of age. The recurrence rate for patients aged less than 70 years fell from 24 to 12 per cent at 3 years ($P=0.001$), but for patients over 70 years it only decreased from 18 to 12 per cent at 3 years ($P=0.2$). For patients under 70 years the DFS improved from 72 to 81 per cent at 3 years ($P=0.02$). The younger group of patients was the one in which management had altered significantly between the two time periods: there was an increased rate of axillary surgery (47 to 74 per cent; $P<0.0001$), and more frequent use of tamoxifen (74 to 84 per cent; $P=0.004$) and chemotherapy (10 to 27 per cent; $P<0.0001$) in this age group.

Discussion

Most reports of the outcome of breast cancer refer to selected patients often as part of randomized trials^{1,2}. Such studies provide valuable information on which to base management guidelines for breast cancer, but outcome in these trials may

not be representative. Regional cancer registry data have the potential to provide more representative outcome information^{3,4} but at present the information available is limited. For example, many are unable to provide stage and grade at presentation or disease recurrence rates^{3,4}. There is also under-reporting of treatment modalities⁷. A registry such as the BBCR, which also includes patients with metastatic disease at presentation (4 per cent) and those treated with tamoxifen alone (8 per cent), can identify any local diagnostic, management or resource problems and provides accurate data for outcome from a single institution when sufficient patients have accumulated.

The most encouraging finding is the improved outcome for more recently treated patients. Overall DFS improved from 70 to 79 per cent at 3 years, with the recurrence rate falling from 22 to 12 per cent (Fig. 1). There are several possible explanations for these findings. First, it is possible that the differences in outcome represent unfair comparison between the two groups, owing to a type II error. For example, follow-up for the more recent time interval was less complete, as demonstrated by the decrease in number at risk between 24 and 36 months in patients diagnosed from 1993 to 1996 (Figs 1 and 2). However, even at 24 months, where follow-up was comparable, there was a difference between the outcome of the two groups. In addition, improved results were apparent in the more recent time interval on multiple regression analysis. Ideally longer follow-up is required in both groups.

The improved outcome in the more recent time interval may reflect a general improvement in the results of breast cancer treatment, as has been reported for England and Wales⁸. Cancer registry data suggested that improved outcome for breast cancer in East Anglia was principally a result of earlier presentation, since there was no stage-specific reduction in mortality rate⁷. However, in Bedford patient outcome has improved despite no significant change in tumour stage or grade at presentation, and the recurrence rate has fallen both for tumours with a favourable and an unfavourable prognosis.

Since 1993 there has been an increase in the frequency of axillary dissection and more frequent use of systemic therapy (Table 2). Even before 1993 tamoxifen treatment was used more commonly in Bedford (80 per cent) than reported for East Anglia (30 per cent)⁷, but at a similar frequency to that reported for Edinburgh (79 per cent)⁹. Meta-analysis suggests that tamoxifen reduces the annual risk of breast cancer recurrence by 30 per cent¹⁰, so the increase in tamoxifen use from 80 to 88 per cent could only explain a small part of the improvement in outcome. Polychemotherapy has similarly been shown to reduce the risk of recurrence by 30 per cent¹⁰, and the large increase in the use of chemotherapy in younger patients may be

significant, particularly since it is this group in which outcome has improved. The recent increase in axillary dissection rate may have had a direct role in improving outcome or may simply allow better selection of patients for systemic therapy¹¹.

It has been suggested that specialization of breast cancer services may influence outcome. It would be difficult to design a randomized trial to investigate this hypothesis, since it would be almost impossible to control for all the variables likely to affect outcome. Gillis and Hole¹² reported a 9 per cent improvement in 5-year survival for patients with breast cancer treated by specialist breast surgeons in Scotland. Such a difference probably reflects variable implementation of optimum local and systemic therapy, since management has been shown to vary considerably in patients with similar tumours treated by different physicians^{13,14}. The present study investigated the effect of specialization in a single district. Given the time differences between the two groups it is possible that improvements in outcome simply reflect changes in disease characteristics which specialization did not influence. However, the finding of a stage-specific advantage in association with changes in treatment suggests that specialization has been an important factor. Surgical subspecialization and the development of protocols to guide management has been associated with the increased rate of axillary dissection and the subsequent use of tamoxifen and chemotherapy detailed above. These changes are the most likely explanation for the improved outcome¹⁵. Whether subspecialization had a beneficial effect on the choice or conduct of operative intervention is difficult to assess. However, increased awareness of the importance of clear surgical margins may have had an impact on the reduction in locoregional recurrence rate from 22 to 12 per cent at 3 years.

The prognostic risk factors for breast cancer are well known¹⁶. However, the present analysis of risk factors for local recurrence and DFS confirms the importance of tumour grade, a feature often ignored in the past. Locoregional recurrence was around seven times more likely for patients with poorly differentiated tumours. The outcome for patients with positive axillary nodes in addition to a poorly differentiated tumour was particularly bleak, with a 3-year DFS of only 50 per cent. In contrast, patients presenting with a screen-detected cancer had an excellent prognosis, with DFS of 94 per cent at 3 years.

This study provides encouragement for patients with breast cancer. Outcome is improving in line with changes in treatment strategies and specialization. The favourable outcome of patients with a screen-detected cancer suggests that there is a likelihood of further improvement in results as more cancers are detected by this method.

Acknowledgements

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Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy

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Background: Despite increasingly radical surgery for oesophageal cancer, many patients continue to develop recurrent disease. The aim of this study was to evaluate the pattern of failure following attempted curative oesophagectomy with two-field lymphadenectomy for adenocarcinoma and squamous cell carcinoma of the middle and lower third of the oesophagus.

Methods: A total of 176 consecutive patients discharged from hospital following R₀ resection between 1 April 1990 and 31 December 1999 were followed for evidence of recurrence over a mean interval of 26 months.

Results: Adenocarcinoma was the predominant histological subtype ($n = 113$) compared with squamous cell carcinoma ($n = 63$). Sex and age distribution were similar for both histological subtypes (M:F ratio 2.5:1, median age 64 (range 40–77) years). Overall 2- and 5-year survival rates were 54 and 31 per cent respectively. Some 85 patients (48 per cent) developed proven recurrence, of whom five are alive and 80 dead. The median time to recurrence was 11.7 (range 1.5–67) months, with a median survival thereafter of only 2.7 (0–25.9) months. The pattern of recurrence was locoregional in 27 per cent (mediastinal 21 per cent and cervical 6 per cent) and distant in 18 per cent (liver 6 per cent, bone 6 per cent, cerebral 2 per cent, peritoneal 2 per cent, lung 1 per cent, skin 1 per cent). There was no difference in the overall pattern of dissemination or timing of recurrence for either histological subtype. Over 50 per cent of all recurrences occurred within 12 months of surgery, with local, regional and distant recurrence occurring at a median of 11.9 (range 1.8–52), 11.0 (range 5–67) and 11.0 (1.5–58) months respectively.

Conclusion: The low incidence of cervical recurrence suggests that a more extensive 'three-field' lymphadenectomy is unlikely to improve survival rates. Better staging modalities are needed to identify patients who will have recurrence within 12 months of operation, so that they may be either entered into trials of multimodality treatment or offered non-surgical palliation.

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Introduction

Surgical resection remains the primary treatment modality for oesophageal carcinoma as it provides sustained palliation of dysphagia and the best chance of cure. Over the past 10 years advances in surgical and anaesthetic techniques, together with improvements in perioperative management, have reduced the risks of oesophageal resection to an acceptable level. This reduction in the postoperative mortality rate has, however, failed to translate itself into any significant benefit in long-term survival as large numbers of patients continue to present with recurrent disease following apparently curative surgery. Attempts

have therefore been made to improve the outcome of surgical resection by increasing the radicality of nodal dissection and, more recently, by combining surgery with other treatment modalities.

However, before embarking upon more extensive surgical procedures or designing adjuvant therapeutic regimens, the pattern of failure of current curative surgical strategies must first be understood. Many surgical series do not adequately document the timing and pattern of recurrent disease, and those that do have originated from Japan and China where squamous cell carcinoma (SCC) rather than adenocarcinoma is the predominant histological subtype. This latter histological subtype now accounts for

over half of all oesophageal cancers in Western practice¹. In addition many studies include a variety of different surgical approaches and varying levels of lymphadenectomy. This paper presents the results of attempted curative two-phase subtotal oesophagectomy with a standardized two-field lymphadenectomy with the aim of determining the pattern and timing of recurrent disease and of assessing the factors that influence this clinical problem and future therapeutic strategies that may decrease it.

Patients and methods

Some 520 patients underwent surgical evaluation for oesophageal malignancy under the care of one surgeon in this institution between April 1990 and December 1999. Of these, 216 consecutive patients had a subtotal oesophagectomy with two-field lymphadenectomy, giving a resectability rate of 42 per cent. Overall 30-day and in-hospital mortality rates were 2 and 4 per cent respectively. Of the 207 patients surviving surgery, data were excluded for 17 patients having palliative resections who had sustained preoperative perforation ($n = 11$) or had evidence of macroscopic residual disease at the time of operation ($n = 6$). Data were also excluded for eight patients who had rare tumours (five leiomyosarcomas, one carcinoid, one small cell carcinoma and one lymphoma) as well as from a further six patients who had received neoadjuvant chemoradiotherapy as part of a separate study.

In the 176 patients who had undergone a potentially curative resection and who were discharged from hospital, the male to female ratio was 2.5 : 1 and the median age 64 (range 40–77) years. Adenocarcinoma was the predominant histological subtype compared with SCC, in the ratio of 2 : 1. There was an even distribution of SCC between the middle and lower thirds of the oesophagus, whereas the majority of adenocarcinomas were located within the lower third (Table 1).

The detailed resection techniques have been described elsewhere². The main steps of the operation include an initial upper midline laparotomy through which the stomach is mobilized based on a vascular pedicle of the right gastric and gastroepiploic arteries. The lesser omentum is divided, encompassing nodes along the lesser curve and those at the origin of the coeliac trunk. The common hepatic artery and the roots of the splenic and left gastric arteries are also skeletonized by complete removal of the surrounding nodal tissue. Following division of the left gastric artery at its origin, an *en bloc* hiatal dissection is performed removing the left and right paracardial stations together with the respective crura. Each nodal group is marked with a silk suture to aid identification when the stomach is delivered into the chest. Via a fifth interspace

Table 1 Distribution of tumours according to histological subtype and site in 176 patients discharged from hospital following attempted curative oesophagectomy

	Middle third	Lower third	Total
Adenocarcinoma	21 (12)	92 (52)	113 (64)
SCC	31 (18)	32 (18)	63 (36)
Total	52 (30)	124 (70)	176 (100)

Values in parentheses are percentages. SCC, squamous cell carcinoma

right thoracotomy, the oesophagus is mobilized, baring the aorta and pulmonary veins of any connective tissue and encompassing the mediastinal pleura. A meticulous lymphadenectomy of the paratracheal, carinal and left and right bronchial nodes is performed followed by *en bloc* resection of the thoracic duct together with the para-aortic nodes. The oesophagus is transected at the level of the thoracic inlet and the stomach delivered into the chest. Sleeve resection of the lesser curve and the associated nodes is undertaken together with the previously marked lymph nodes and a stapled oesophagogastric anastomosis fashioned. The nodes in the aortopulmonary window are removed but a full dissection of the left recurrent laryngeal nerve chain is not routinely carried out. No cervical lymphadenectomy is undertaken.

All nodal material is dissected separately from the specimen at the end of the procedure and analysed in accordance with the guidelines of the Japanese Research Society for Oesophageal Diseases³. Tumour node metastasis (TNM) classification was performed using the fifth edition of the Union Internacional Contra la Cancerum⁴. In cases of superficial tumours, two independent experienced gastrointestinal pathologists carried out the distinction between high-grade dysplasia and mucosal carcinoma.

In the early part of the study period 19 selected patients with poor histopathological prognostic features also received adjuvant radiotherapy, although this was abandoned in 1992 when large randomized trials demonstrated no benefit from this approach^{5,6}.

All patients surviving operation were followed until death or the present day, at 3-month intervals in year 1, 6-month intervals in year 2, and annually thereafter. At each follow-up appointment a thorough physical examination was carried out. If recurrence was suspected, patients underwent thoracoabdominal computed tomography (CT) and endoscopic examination. More selective investigations such as cervical ultrasonography, bone scintigraphy and cerebral CT were carried out based on specific symptomatology, clinical examination and biochemical profile. All cases of unexplained or sudden death were referred for post-mortem examination. No patient was lost to follow-up.

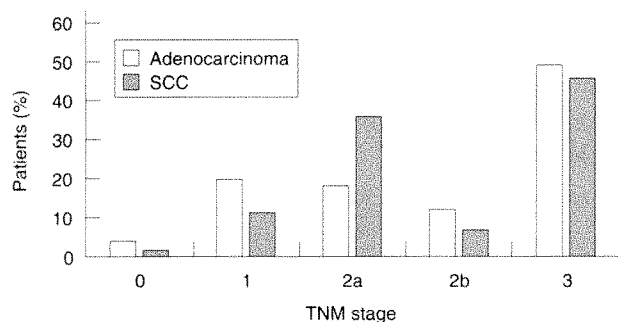


Fig. 1 Percentage of patients with each histological subtype in relation to pathological tumour node metastasis (TNM) stage of resected specimen following potentially curative oesophagectomy. SCC, squamous cell carcinoma

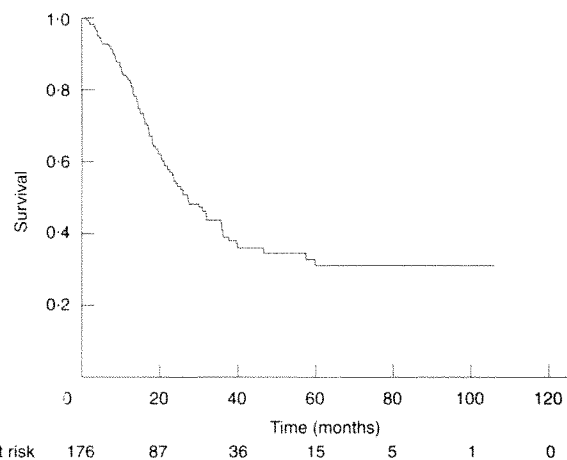
Local recurrence was defined as that occurring in the mediastinum or upper abdomen at the site of previous oesophageal resection and nodal clearance. Regional recurrence was defined as that occurring in the cervical area where no lymphadenectomy had been performed. Distant recurrence was defined as haematogenous if it developed within a solid organ, or as transcoelomic if it was within the peritoneal cavity. Histological, cytological or unequivocal radiological proof was required before a diagnosis of recurrence was made. Recurrence supported by clinical impression alone was not included. If recurrence was found at more than one site on initial investigations or was subsequently detected at another site within 30 days, it was defined as occurring synchronously in both areas.

All data were collected prospectively on a Microsoft Access (Redmond, Washington, USA) database. Statistical analysis was performed using χ^2 , log rank and Mann-Whitney *U* tests.

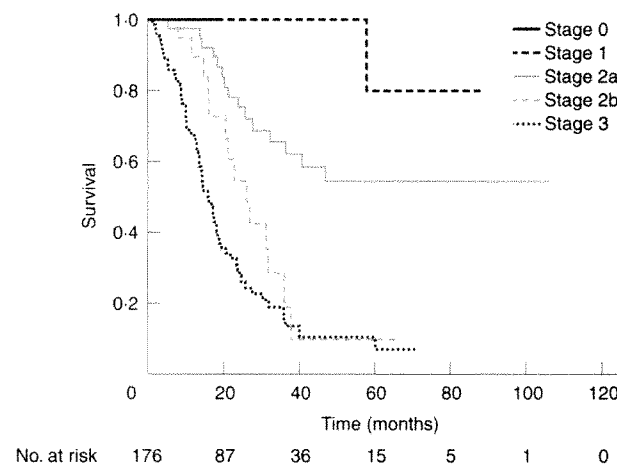
Results

Histopathological staging of the resected specimens according to the current TNM staging classification demonstrated a predominance of full-thickness tumours with nodal disease, with no statistical difference in stage distribution between adenocarcinomas and SCCs (Fig. 1). The mean follow-up interval was 26 (range 1–109) months. The overall survival rate at 1 year was 83 per cent, at 2 years 54 per cent and at 5 years 31 per cent (Fig. 2a). Stratification of survival according to the TNM staging system confirmed a significantly worse survival for more advanced tumours (Figure 2b).

To date, 93 patients have died during the follow-up period, 80 as the result of proven recurrent oesophageal carcinoma and 13 from causes other than recurrence with unequivocal confirmation on post-mortem examination.



a Overall survival



b Stage-specific survival

Fig. 2 a Overall survival following discharge for 176 patients undergoing potentially curative radical oesophagectomy; **b** stage-specific Kaplan-Meier survival curves for 176 patients discharged following R_0 resection

The causes of death in this latter group were myocardial infarction (six patients), bronchopneumonia (three), ovarian and rectal cancer (two), cerebral abscess (one) and alcoholic cirrhosis (one), with a median time to death of 14 (range 3–47) months after operation. Of the remaining 83 patients who are currently alive, five are known to have recurrent disease. Thus, 48 per cent (85 of 176) of all patients discharged following potentially curative oesophageal resection have developed recurrent oesophageal cancer. The median time to recurrence was 11.7 (range 1.5–67) months, with over 50 per cent (45 of 85) of all recurrences developing within 12 months of operation (Fig. 3). There was no difference in the disease-free interval

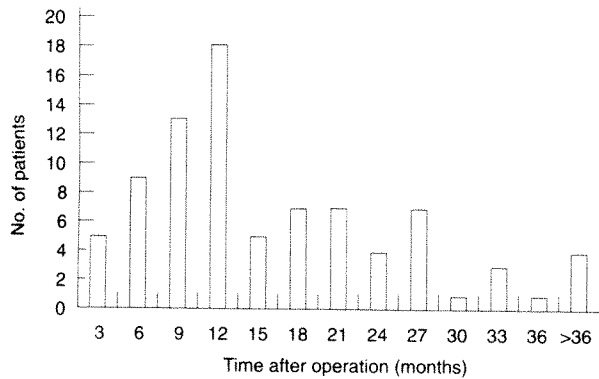


Fig. 3 Timing of detection of recurrent disease following R₀ resection (median 11.7 months). More than 50 per cent of all recurrences were detected within 12 months of operation

Table 2 Distribution by site of patients with recurrent disease

Site of recurrence	No. of patients (n=176)
Local	37 (21.0)
Mediastinal	15
Tracheobronchial	7
Anastomotic	6
Gastric conduit	5
Hiatal or upper abdominal	4
Regional (cervical)	10 (5.7)
Distant	31 (17.6)
Haematogenous	
Liver	11
Bone	10
Cerebral	3
Skin or soft tissue	2
Lung	2
Transcoelomic	
Peritoneal	3
Multiple sites	7 (4.0)
Total	85 (48.3)

between adenocarcinoma and SCC, or between middle-third and lower-third lesions.

The pattern of recurrence is shown in Table 2, with a similar proportion of local and distant dissemination (21 and 18 per cent respectively). Regional (cervical) recurrence occurred in ten patients (6 per cent), seven of whom had undergone resection for lower-third adenocarcinoma and three for middle-third SCC. All ten patients with cervical recurrence had node-positive tumours at the time of operation. A further seven patients (4 per cent) developed synchronously detected recurrent disease at initial investigation in both the mediastinum and at distant sites. Thus, the overall incidence of recurrent disease in areas outside the operative field was 27 per cent. Distant dissemination

Table 3 Incidence of recurrence in relation to tumour site and histological subtype

	Type of recurrence			
	Local	Regional	Distant	Synchronous
Site				
Lower third (n=124)	24 (19)	7 (6)	24 (19)	4 (3)
Middle third (n=52)	13 (25)	3 (6)	7 (14)	3 (6)
Histological subtype				
Adenocarcinoma (n=113)	21 (19)	7 (6)	22 (20)	4 (4)
SCC (n=63)	16 (25)	3 (5)	9 (14)	3 (5)

Values in parentheses are percentages. SCC, squamous cell carcinoma. There were no significant differences between the groups (Chi squared test).

rather than locoregional recurrence occurred more frequently with lower-third tumours (predominantly adenocarcinoma) whereas the converse was true of middle-third lesions (predominantly SCC). However, there was no significant difference in the overall pattern of recurrence in relation to either the level of the primary tumour or its histological subtype (Table 3).

The median time to local recurrence was 11.9 (range 1.3–52) months, the median time to regional recurrence was 11 (range 5–67) months, and that for distant recurrence was 11 (range 1.5–58) months. Median survival following the detection of recurrent oesophageal cancer was 2.4 (range 0–25.9) months, and was similar for distant dissemination (median 1.8 (range 0–14.6) months) and local recurrence (median 2.7 (range 0–13.2) months). Median survival in patients with regional cervical recurrence was 10.5 (range 2–25.9) months and was significantly longer than in those with recurrence at other sites ($P=0.01$).

Half of the patients with local recurrence had no specific treatment other than pain control. Patients with dysphagia due to anastomotic, conduit or hiatal recurrence were palliated with dilatation and endoprosthesis insertion with or without subsequent endoluminal or external-beam radiotherapy, depending on their general condition. The majority of patients with distant organ metastasis received no definitive therapy other than symptomatic relief. Six patients with bone metastases underwent palliative radiotherapy or orthopaedic fixation, three with liver metastases received palliative chemotherapy with 5-fluorouracil and cisplatin, and two with soft tissue or skin deposits had these excised. No survival advantage was observed in patients who were selected for interventional therapy compared with those who had symptomatic treatment alone. Recurrent laryngeal nerve palsies resulting from cervical recurrence were treated with Teflon (Du Pont, Stevenage, UK) injection in three cases, and more latterly with Issik thyroplasty in five patients. Two patients with isolated

Table 4 Prognostic factors associated with the development of recurrent disease

	Recurrence (n=85)	No recurrence (n=91)*	P†
Median age (years)	64	64	n.s.
Sex ratio (M:F)	3:1	2.2:1	n.s.
Depth of invasion			
≤ T ₂	16 (19)	57 (63)	
≥ T ₃	67 (79)	36 (40)	< 0.001
Node positive	71 (84)	30 (33)	< 0.001
Degree of differentiation			
Well	8 (9)	41 (45)	
Moderate	30 (35)	33 (36)	
Poor	47 (55)	17 (19)	< 0.001
Perineural invasion	40 (47)	23 (25)	0.002
Vascular invasion	17 (20)	11 (12)	n.s.
Lymphatic invasion	25 (29)	14 (15)	0.0016

Values in parentheses are percentages. *Includes 13 patients who died without evidence of recurrent oesophageal cancer. n.s., Not significant.

†Mann Whitney U and Chi squared tests

asymptomatic recurrent cervical nodal disease have had ipsilateral radical cervical lymph node clearance and are currently still alive. The remaining eight patients with cervical recurrence eventually died as the result of distant dissemination in five cases and local tracheobronchial obstruction or fistulation in three. The relative survival advantage observed in patients with cervical recurrence is described above.

Prognostic factors that potentially influence recurrent disease are analysed in *Table 4*. Increased depth of tumour invasion and the presence of nodal metastases were found to correlate with an increased incidence of recurrent disease, although there was no association with the site of recurrence. On histopathological grounds, the presence of perineural and lymphatic invasion together with worsening tumour differentiation were similarly linked to the subsequent development of recurrent disease. Of the 19 patients who received postoperative adjuvant endoluminal radiotherapy in the early part of the series, 17 subsequently developed recurrence with no differences noted in either the timing or the pattern of recurrence for these patients compared with that in those who received no adjuvant therapy. The six patients with anastomotic recurrence all had advanced stage 2b–3 tumours, although none had any evidence of proximal resection margin involvement, with a similar degree of clearance compared with those who did not develop anastomotic recurrence.

Discussion

At a mean follow-up of 26 months, recurrent oesophageal cancer had developed in almost half of all patients who

underwent an apparently curative resection, with an overall 5-year survival rate of only 31 per cent. These dismal results occurred in an already highly selected patient group who had been staged as having localized and resectable tumours and were also considered sufficiently young and fit to withstand major thoracoabdominal surgery. As a result, the overall survival figures for all patients with oesophageal cancer are extremely poor. Less than 10 per cent of European patients with oesophageal cancer are alive at 5 years⁷, which reflects the advanced nature of the disease at presentation.

While it is evident from the stage-specific survival figures presented here that early tumours, particularly those that are node negative, are associated with a low incidence of recurrence and a significant survival advantage, they are found in only a minority of patients undergoing surgery. Attempts to shift the balance in favour of such tumours by the wider use of open-access endoscopy services⁸ and Barrett's surveillance programmes⁹ have led to increasing numbers of patients with early tumours. However, despite adopting such an approach over a 10-year period, only 20 per cent of all potentially curative resections in this series were performed for stage 0–1 disease. Instead, strategies aimed at decreasing the recurrence rate and improving survival must continue to focus on the majority of patients who present with advanced oesophageal cancer.

Radical lymphadenectomy, widely adopted in Japan for both gastric adenocarcinoma and oesophageal squamous carcinoma, has been cited as a means of improving the prognosis for patients with upper gastrointestinal malignancy¹⁰. The proponents of these techniques suggest that meticulous nodal dissection improves pathological tumour staging, enhances local control, and may provide some survival benefit in terms of delay to recurrence and even long-term cure. The present authors have reported a 21 per cent local recurrence rate following radical resection for middle- and lower-third tumours, which is lower than that described in other series where no formal lymphadenectomy was performed¹¹. Furthermore, despite the strong association between nodal disease and tumour recurrence, some node-positive patients were long-term survivors, with 5-year survival rates of 10 and 7 per cent for stage 2b and stage 3 tumours respectively. Although the efficacy of radical lymphadenectomy cannot be proven by such data, the present findings are similar to those of other groups adopting a two-field nodal clearance for both SCC^{2,12} and adenocarcinoma¹³. The latter study demonstrated a significant survival benefit for node-positive patients, with 34 per cent of those undergoing *en bloc* oesophagectomy alive at 3 years, compared with only 13 per cent of patients who had no formal lymphadenectomy.

In an effort to improve the results of surgery still further, the Japanese have advocated the addition of cervical lymphadenectomy to conventional thoracoabdominal lymph node dissection. Drainage to the bilateral cervical nodal chains from the thoracic oesophagus is certainly known to occur and has been demonstrated by elegant experiments using technetium uptake¹⁴. An overall rate of 30 per cent for cervical nodal disease has been documented for SCC of the oesophagus by three-field nodal dissection¹⁵. Cervical lymph node disease was found in 60 per cent of upper-third, 20 per cent of middle-third and 12.5 per cent of lower-third tumours¹⁶. In the present series, isolated cervical recurrence occurred in only ten patients (6 per cent), only three of whom had SCC, suggesting a much lower incidence of positive cervical nodes than described previously. However, cervical nodal disease at the time of operation may not correspond with subsequent clinical recurrence and may instead be a manifestation of systemic disease with distant recurrence ultimately leading to symptoms and death. Against this theory is the significantly longer survival experienced by patients with cervical recurrence in the present series (median 10.5 months *versus* 2.4 months overall survival). This would favour the concept that cervical nodal recurrence is a source of subsequent tumour spread and not merely a reflection of disease that has already disseminated, although such a mechanism of metastatic spread has in the past been considered exceptional¹⁷.

The majority of patients who developed cervical recurrence in this series had, surprisingly, undergone resection for lower-third adenocarcinoma. Most, if not all, adenocarcinomas arise within Barrett's epithelium in the distal oesophagus¹⁸ and a much lower incidence of cervical disease would therefore be expected when compared with SCC, which is usually sited more proximally. Adenocarcinoma of the oesophagus is predominantly a Western disease and few studies have addressed the role of cervical nodal dissection in the management of such tumours. In a prospective trial of three-field lymphadenectomy for both histological subtypes, Altorki and Skinner¹⁹ found four patients with cervical nodal metastases from lower-third adenocarcinomas in the absence of any mediastinal or upper abdominal nodal disease. In contrast, all ten patients who developed cervical recurrence in the present series already had nodal disease within the mediastinal or upper abdominal fields at the time of operation. Any potential benefit from cervical lymphadenectomy must be balanced against the additional morbidity and mortality, particularly related to recurrent laryngeal nerve damage. This significant complication may occur more commonly in cervical dissection in Western patients, who tend to be more obese than their Eastern

counterparts, thus outweighing any potential survival benefit in what appears to be a very small group of patients.

Alternative strategies to decrease recurrence and improve survival have therefore turned away from increasingly radical surgery and focused more on multimodality therapy. Distant haematogenous recurrence occurred in 16 per cent of patients in this series, suggesting that many of these patients had micrometastatic disease at the time of resection. Indeed, one recent prospective study in which marrow trephine was performed in patients with operable oesophageal cancer demonstrated micrometastases in 88 per cent of rib and 15 per cent of iliac bone marrow aspirates²⁰. Surgery as a single modality therapy, irrespective of the degree of nodal clearance, can be considered only as a local treatment. Systemic treatment of potentially disseminated disease may be accomplished by the use of chemotherapy, particularly if administered in the neoadjuvant setting, and the results of the British Medical Research Council trial examining this approach are awaited. Furthermore, the fact that certain chemotherapeutic agents act as radiation sensitizers has led to considerable interest in the combination of neoadjuvant chemoradiotherapy as a means of enhancing locoregional disease, in addition to providing systemic therapy²¹⁻²³. Despite meticulous nodal clearance with maximal *en bloc* resection, local recurrence still occurred in 21 per cent of patients in the present series and thus neoadjuvant chemoradiotherapy would appear to be a logical approach for both histological subtypes. While the results of three large randomized controlled trials²¹⁻²³ performed to date are conflicting and open to criticism, this approach is currently the most promising, although until proven it should be applied only within the context of a clinical trial.

Adjuvant therapy, in the form of endoluminal radiotherapy, was administered in the early part of this study to 19 patients and was not found to defer recurrence or improve survival. This is in keeping with the findings of two large randomized clinical trials that also failed to demonstrate any overall benefit from a similar approach^{5,6}. The former of these trials showed some improvement in locoregional control, from a 35 to a 10 per cent failure rate⁵, but this was confined only to node-negative patients, a group that in this series already had a very low incidence of any form of recurrence. The second trial⁶ demonstrated that adjuvant radiotherapy reduced local recurrence only for a small subgroup of patients who had had palliative resections with residual macroscopic disease around the tracheobronchial tree. Neither trial demonstrated any overall survival benefit.

The lack of any benefit for adjuvant radiotherapy is consistent with the disappointing median survival time following diagnosis that was noted for the majority of

patients in the present study who developed recurrent disease. Excluding the small number of patients with isolated cervical recurrence, no specific treatment provided any significant improvement in survival. This is in concordance with the published data suggesting that serial postoperative CT may detect recurrence several months in advance of symptoms, but such information will have no impact on overall outcome^{24,25}. The present findings of a strong association between recurrence and TNM stage, together with various other pathological features in resected specimens, as noted by other authors^{25,26}, would thus appear to have little clinical value. Whilst such information may be useful in counselling patients and relatives, proven adjuvant therapeutic options are lacking.

Instead, patients at high risk of developing recurrence need to be identified in the preoperative staging process. With the wider use of high-quality endoscopic ultrasonography, the accuracy of staging information may improve such that patients at high risk of recurrence may be identified. These patients are unlikely to be cured by surgery alone and are the very candidates who would be suitable for entry into trials of multimodality therapy. However, given the risks of oesophageal resection, together with the long recovery period and its significant impact on quality of life²⁷, the identification of patients who might recur early, dying within 12 months of operation (17 per cent in this series), may prompt the clinician to consider the option of non-surgical palliation.

In conclusion, most patients with oesophageal cancer in the UK continue to present with advanced disease, and radical surgery alone fails the majority of such individuals. Based on the low incidence of cervical recurrence in this series, it is suggested that the addition of more radical bilateral cervical lymphadenectomy would have little impact on survival and must be balanced against increased morbidity and cost. Instead, strategies aimed at improving the outcome for this distressing disease must focus on earlier diagnosis and improved staging modalities. Patients at high risk of recurrence and early death need to be identified accurately before operation such that they may be offered entry into trials of multimodality therapy or alternatively considered for non-surgical palliation.

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Major intra-abdominal pathology missed at laparoscopic cholecystectomy

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Introduction

Laparoscopic cholecystectomy has been shown to be an effective and safe treatment for symptomatic cholelithiasis. There have, however, been reports of serious intra-abdominal disease present, but not identified, at the time of operation¹⁻⁴. Resultant delay in diagnosis often necessitates further surgical intervention, and in cases of malignancy may affect potential curability. Missed malignant primary lesions have included the colon, pancreas, stomach and lower oesophagus. The commonest reported missed benign disorder has been that of Crohn's disease. Data quantifying the extent of this potential problem are limited. This study aimed to evaluate its incidence in a large teaching hospital over an extended period of time.

Patients and methods

Patients undergoing laparoscopic cholecystectomy between September 1994 and September 1997 were identified using the Lothian Surgical Audit database, which has stored detailed data on all surgical patients in the Lothian region of Scotland since 1991. Of 695 identified patients, those readmitted within 12 months of laparoscopic cholecystectomy for either investigation or treatment of further intra-abdominal pathology were assessed in detail to identify new diagnoses and, if so, whether symptoms present before cholecystectomy could be attributed to the newly diagnosed condition. As surgical details of the whole Lothian region are captured on the Lothian database, run by dedicated data collectors, the likelihood of not identifying cases of missed major intra-abdominal pathology within the region captured by the database was small.

Results

Four patients (0.6 per cent) (two men; age range 30-66 years) were identified. All had advanced malignant disease, and only two were potentially curable at the time of ultimate diagnosis. There were no patients with missed major benign pathology.

Two right colonic carcinomas (hepatic flexure, proximal ascending colon) occurring in patients aged 30 and 45 years were noted to be 'bulky' at laparotomy, but were resected with curative intent. Both patients received postoperative chemotherapy. The former (Dukes B tumour) had complete local excision of a large abdominal wall recurrence at 24 months, and was well and disease free 2 months later. The latter patient (Dukes C tumour) was asymptomatic at 31 months, but had a rising carcinoembryonic antigen level suggestive of recurrent disease. One periampullary carcinoma with nodal spread and one locally advanced pancreatic head carcinoma were irresectable on diagnosis, and managed by palliative stenting at endoscopic retrograde cholangiopancreatography, the latter following diagnostic laparoscopy with ultrasonography. The former patient went on to require surgical biliary bypass. Both died from disseminated disease 5 and 10 months after diagnosis.

The mean interval from laparoscopic cholecystectomy to ultimate diagnosis was 3.8 (range 1-7) months. All patients had preoperative intermittent upper abdominal pain, three being colicky in nature, with persisting unaltered symptoms after operation. All had cholelithiasis documented before operation on ultrasonography and confirmed at operation, and histological evidence of chronic cholecystitis in surgical specimens.

Discussion

Although accepted as the treatment of choice for symptomatic cholelithiasis, a potential disadvantage of laparoscopic cholecystectomy is the lost ability to palpate the abdominal organs which the formal laparotomy of open cholecystectomy previously allowed. This may result in failure to identify concurrent intra-abdominal pathology producing symptoms attributed to cholelithiasis which led to operation in the first place. Symptoms frequently attributed to gallstones are not specific to biliary pathology, and sonographic evidence of cholelithiasis on investigation does not necessarily confirm a causal relationship. Patients should be selected carefully for laparoscopic cholecystectomy on the basis of a typical biliary history in the presence of documented cholelithiasis, and supportive clinical and biochemical findings. Patients with atypical symptoms or findings warrant a more detailed preoperative assessment for alternative aetiologies.

There have been limited reports of missed major intra-abdominal pathology at the time of laparoscopic cholecystectomy¹⁻⁴, but the incidence of such pathologies has infrequently been quantified. Hanney *et al.*¹ reported a rate of less than 1 per cent in 534 patients, with four of five cases identified within 4 months of operation. Two had advanced malignancy with early death, and three had complicated Crohn's disease requiring surgical resection. Slim *et al.*²

reported four right colonic and three pancreatic carcinomas missed in 838 patients (0.8 per cent), but did not report on missed benign pathologies. Gal *et al.*³ reported three missed carcinomas (two colonic, one gastric) and one case of small bowel mesenteric fibrosis in 676 patients (0.6 per cent), all identified within 7 months of laparoscopic cholecystectomy. Denning and Lipshy⁴ reported a missed diagnosis rate of 2.6 per cent in 894 patients within 10 months of laparoscopic cholecystectomy, 40 per cent of which were intra-abdominal malignancies.

This series reports an incidence of missed major pathology of 0.6 per cent, with all cases identified within 7 months of laparoscopic cholecystectomy. Supporting the findings of others^{1,2}, tumours were advanced at diagnosis, with reduced potential for cure. Persistence of symptoms after operation suggests that gallstones identified before operation were incidental, and that preoperative symptoms were related to the underlying tumours. It also highlights that, if symptoms for which laparoscopic cholecystectomy was performed do not resolve, patients should be reviewed carefully and reinvestigated to exclude a missed diagnosis.

Diagnostic laparoscopy yields positive findings in up to 76 per cent of patients when evaluating chronic abdominal pain⁵ and is effective in the diagnosis, staging and exclusion of intra-abdominal malignancy. If applied routinely during laparoscopic cholecystectomy it may help overcome potential limitations caused by loss of visceral palpation. In this series, the periampullary and both the colonic carcinomas were noted to be 'large' or 'bulky', suggesting they might

have been identified if formal visceral laparoscopy had been performed at the original procedure. The frequently advanced nature at diagnosis of missed tumours, and the usually obvious serosal macroscopic features of complicated Crohn's disease, lend these lesions to more likely identification at laparoscopy. Although the expected pick-up of concurrent major intra-abdominal pathology would be low, it would be a useful intraoperative routine at the time of laparoscopic cholecystectomy.

Acknowledgements

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Changing patterns in the management of gastric volvulus over 14 years

Authors' reply

Sir

We thank Messrs. Daniels and Chisholm for their interest in our paper (*Br J Surg* 2000; 87: 1251-1252). We do agree that laparoscopic treatment of gastric volvulus should be avoided in high risk patients in whom technical difficulties are likely to be encountered. This is certainly the case if either the stomach or oesophagus is likely to be ischaemic, or if the stomach cannot be decompressed by naso-gastric drainage before surgery commences. The situation in which there is 'considerable inflammation' and the oesophagus is 'friable' has been very unusual in our experience. Since commencing laparoscopic repair, all acute patients have been successfully managed by initial naso-gastric tube decompression followed by surgery on the next available elective operating list. We wonder whether the apparent difference between our experience and theirs is due to a difference in referral patterns which could be resulting in later presentation, leading to more difficult pathology being encountered. We have not incorporated colopexy into any of our operative procedures and have not seen any problems arise due to its omission.

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Intraperitoneal polypropylene mesh repair of incisional hernia is not associated with enterocutaneous fistula

Sir

I found the article by Vrijland *et al.* (*Br J Surg* 2000; 87: 348-352) of great interest. However, intestinal fistulae can occur as late as 15 years after intra-abdominal polypropylene implantation^{1,2}. With increasing evidence of mesh related intestinal complications, drawing such a powerful conclusion based on a short-term follow-up of six years can lead to hazardous consequences for the patients and serious liabilities for the surgeons. Many experimental models have been used to address these serious problems using a variety of absorbable biomaterials in combination with polypropylene mesh. Each

study demonstrated that absorbable/non-absorbable composites can only reduce the quantity and grade of adhesions and none reported complete elimination.

In 1994, I and others suggested covering the visceral side of the mesh with a layer of non-absorbable and tissue impervious biomaterial and in an animal study there was successful and complete elimination of adhesion formation³. For this purpose, a variety of tissue impervious biomaterials such as polypropylene film and submicronic pore size ePTFE are available. A commercially available version of such combinations consists of polypropylene mesh on the parietal side and a layer of tissue impervious ePTFE on the visceral side. These combinations provide an excellent parietal surface for tissue in-growth while avoiding intestinal adhesion on the visceral side. It would not seem sensible to accept the risk of plain polypropylene, no matter how small it is.

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- 1 DeGuzman LJ, Nyhus LM, Yared G, Schiesinger PK. Colocutaneous fistula formation following polypropylene mesh placement for repair of a ventral hernia: diagnosis by colonoscopy. *Endoscopy* 1995; 27: 459-61.
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Authors' reply

Sir

We thank Dr Amid for his valuable comments and agree that a longer follow-up would strengthen our conclusion. Although we acknowledge that enterocutaneous fistulae can become apparent more than 6 years after intraperitoneal mesh placement we do not expect a sudden onset of this problem after a 'dormant' period of 6 years. The composite mesh as described by Dr Amid appears associated with distinct benefits and we anxiously await the outcome of clinical employment of this novel mesh.

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Benign Disorders and Diseases of the Breast — Concepts and Clinical Management. 2nd Ed.

E. Hughes, R. E. Mansel, D. J. T. Webster

282 × 223 mm. Pp 316. Illustrated 2000. London W B Saunders. £60.00

This book, now in its second edition, dealing with benign disorders of the breast and benign breast diseases was first published in 1989. As Kirby Bland states in the foreword of this new edition 'The authors elucidate the characteristics of these conditions in their own right and do not focus attention solely on the exclusion of neoplastic disease and/or cancer risk'. This does not mean that no links are made to malignancies of the breast. For example, in the new last chapter dealing with psychological aspects, it is clearly stated that the most common interaction between benign breast disease and the psyche is the development of anxiety as a result of breast symptoms. Another chapter focuses on the risk of cancer of benign disorders. Most important, however, is that the authors consider most of the disorders of the breast as aberrations of normal development and involution (ANDI). This concept is becoming more and more accepted and proves to be most fruitful in understanding benign diseases. A criticism is that insufficient importance is attached to the increasing significance of magnetic resonance imaging in the differential diagnosis of breast diseases, particularly between fibroadenoma, cyst and malignancy; but this does not influence the eventual appreciation of the work. The power of the book is that it gives anyone involved with benign or malignant breast pathology a comprehensive insight into the aetiology, as well as the management of benign disorders. It is clearly written and richly illustrated with high quality photographs in full colour. Every chapter starts with key points and new developments, and ends with many relevant references. This unique book is wholeheartedly recommended.

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Atlas of Surgical Stapling

W. Feil, H. Lippert, P. Lozac'h, G Palazzini (eds)

310 × 220 mm Pp 294. Illustrated 2000. Heidelberg: Johann Ambrosius Barth. DM 255.

This interesting atlas deals with surgical stapling in the whole gastrointestinal tract and abdomen. Most of the pictures are very well done and it is easy to understand all steps in different anastomoses. However, I feel that many of the procedures shown are not particularly realistic and more a matter of

possible ways to use staplers than practical solutions to real problems. This is especially true for different types of gastric resection. Also among gastric resections an important anastomosis is missing. All drawings show circular staplers to anastomose small bowel to oesophagus but sometimes the oesophagus is tiny and it is risky to introduce a circular stapler; linear staplers may be more appropriate. There is an interesting anastomosis using two straight staplers, one linear cutter and one linear stapler proposed by B. Walther, which produces a convenient oesophagojejunostomy¹. Another omission is the J pouch construction in low anterior resection and discussion about pouch length. If such a pouch is used, it should not be more than 6 cm (data now support this). More precise guidelines are also needed. For instance, in low rectal cancer surgery and pouch surgery for ulcerative colitis it is important that the rectal stump is not too long; this should be mentioned. Although most pitfalls in stapling techniques are recorded in this book, they may be difficult to find as they do not appear in appropriate places. It would be useful to have a special chapter in which avoidance of some of the pitfalls is addressed, such as not using cautery on bleeders on the staple line and always stapling from the antimesenteric to the mesenteric part when using linear cutters. Such discussion might also include pitfalls in placing the purse string suture, crossing staple lines and importantly, how to avoid ischaemic areas when several staple lines cross. Details such as checking the purse string suture are important, but small hints on how to check must be given. Another important omission is how to staple parenchymatous organs such as the liver and spleen. The spleen and pancreas are stapled frequently and this should be covered in a book such as this.

In conclusion, this is an interesting book with many attractive drawings. It allows young surgeons to understand gastrointestinal stapling, but it is important to emphasize that staples just appose tissues, and that dissection technique and the technique of handling organs should be of the same high standard whatever type of suturing method is used. This concept was highlighted in one symposium held at the American College of Surgeons when stapling was new; one of the participants had an interesting slide, 'A fool with a tool is still just a fool'.

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- 1 Walther BS, Zilling T, Johnsson F, Stael von Holstein C, Joelsson B. Total gastrectomy and oesophagojejunostomy with linear stapling devices. *Br J Surg* 1989; 76: 909–912.

Scientific Surgery

Atkin W, Hart A, Edwards R, Cook CF, Wardle J, McIntyre P *et al.* Single blind, randomised trial of efficacy and acceptability of oral Picolax *versus* self administered phosphate enema in bowel preparation for flexible sigmoidoscopy screening. *BMJ* 2000; **320**: 1504–9.

Some 1442 patients were included. Compliance was better with the enema (84 *versus* 79 per cent), as was the quality of bowel preparation (higher proportion of procedures completed to the descending colon).

Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; **355**: 1295–302.
The trial included over 13 000 patients with a fractured femur and over 4000 having a hip replacement. Patients randomly allocated aspirin in addition to standard antithrombotic prophylaxis had the incidence of PE reduced by 45 per cent and DVT by 29 per cent.

Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN *et al.* Conventional dose chemotherapy compared with high dose chemotherapy plus autologous hemopoietic stem cell transplantation for metastatic breast cancer. *N Engl J Med* 2000; **342**: 1069–76.

After initial remission chemotherapy 110 patients were randomized to stem cell therapy and 89 to maintenance chemotherapy. There was no significant difference in three year survival rates (32 per cent after transplantation *versus* 38 per cent in controls).

Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B *et al.* Lack of effect of low-fat, high fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000; **342**: 1149–55.

Some 2079 patients with previous adenoma were randomized to the diet or control groups. During follow-up, 39.7 per cent of subjects in the diet group and 39.5 per cent in the control group developed a further adenoma.

Alberts DS, Martinez ME, Roe DJ, Guillen-Rodriguez JM, Marshall JR, van Leeuwen B *et al.* Lack of effect of a high fiber cereal supplement on the recurrence of colorectal adenomas. *N Engl J Med* 2000; **342**: 1156–62.

Some 1429 patients with a previous colorectal adenoma were randomized to a high or low fibre diet. At median follow-up of three years, the rate of recurrent adenomas was similar: 47 per cent high fibre and 51 per cent in the low fibre diet groups.

Cirera L, Balil A, Batiste-Alentorn E, Tusquets I, Cardona T, Arcusa A *et al.* Randomised clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. *J Clin Oncol* 1999; **17**: 3810–5.

A total of 148 patients with stage III stomach cancer after resection were randomly allocated to additional chemotherapy or control groups. Overall five year survival was better after chemotherapy (56 per cent *versus* 36 per cent, $P=0.04$).

Sykes TCF, Brookes P, Hickey NC. A prospective randomised trial of tourniquet in varicose vein surgery. *Ann R Coll Surg Engl* 2000; **82**: 280–2.

In this trial including 50 patients, a tourniquet reduced perioperative blood loss and bruising but had no effect on pain scores or cosmetic results.

Gupta R, Sinnett D, Carpenter R, Preece PE, Royle GT. Antibiotic prophylaxis for postoperative wound infection in clean elective breast surgery. *Eur J Surg Oncol* 2000; **26**: 363–6.
This multicentre study included 357 patients randomized to single dose prophylaxis with coamoxclav or placebo. Wound infection rates were similar: 13 *versus* 19 per cent, respectively.

Quasar Collaborative Group. Comparison of fluorouracil with additional levamisole, higher dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; **355**: 1588–96.

Four different chemotherapy regimens were evaluated in a study including 4927 patients. Adding levamisole and increasing the dose of folinic acid did not improve the survival rate over conventional chemotherapy.

Early Breast Cancer Trialists Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355**: 1757–70.

Forty trials involving over 20 000 patients were evaluated. Radiotherapy reduced the rate of local recurrence, but in later years some of this advantage was lost by increases in late complications, particularly in the elderly.

Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut* 2000; **46**: 813–8.

Some 101 patients were recruited: postoperative enteral nutrition supplements reduced postoperative weight loss, with improved grip strength and quality of life. They also halved the number of perioperative complications requiring antibiotic treatment.

Wu CT, Yu JC, Liu ST, Yeh CC, Li CY, Wong CS. Preincisional dextromethorphan treatment for postoperative pain management after upper abdominal surgery. *World J Surg* 2000; **24**: 512–7.

Sixty patients were randomized into one of four groups: three different analgesic doses and a control group. Premedication with dextromethorphan produced a dose-dependent reduction in postoperative analgesic requirements.

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

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Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:¹ or ^{1–3}. References cited only in tables or figures should be numbered in sequence.

Living donor liver transplantation: present and future

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Ten years have elapsed since living donation became an accepted option for liver transplantation. In Japan, living donor transplantation developed more rapidly than in other parts of the world and, to date, almost 1000 patients have undergone such a procedure in that country. While the main justification for this rapid development in Japan is the absence of cadaveric donors, it should be appreciated, too, that such expansion is also related to the technical expertise of south-east Asian surgeons in all the fields of liver and biliary surgery. Indeed, such expertise is an absolute necessity for performing hepatectomy in healthy subjects with a minuscule risk of death and an acceptable rate of morbidity. The early demonstration of the safety of the procedure resulted in left hepatectomy for living donation for children and small adults rapidly becoming routine¹.

Interestingly, it became evident that the results of living related transplantation for paediatric recipients were significantly better than those of cadaveric transplantation². This difference was related, contrary to expectation, to factors other than immunological ones, since the need for immunosuppression and the incidence of rejection were not significantly different between patients receiving either living donor or cadaveric grafts². The non-immunological factors that might contribute to these better results are likely to be the good quality of the graft, the very short period of cold ischaemia and the ability to plan the procedure (which can be scheduled for the most experienced surgeons and anaesthetists). There is also the possibility of choosing the optimal timing for the recipient, who may be prepared with preoperative medical interventions such as nutritional support or antibiotics. The good results of living donor transplantation illustrate that these factors outweigh the risks of receiving a partial graft, such as vascular thrombosis (due to the small size of the vessels), biliary complications (due to the small size of biliary anastomoses and to their devascularization) and perioperative bleeding (due to the presence of a parenchymal cut surface).

Although living donation of a left-side graft is now a routine procedure for transplantation in children, the use of living donors for adults is currently considered more problematic; left-side grafts are rarely large enough to be suitable for an adult recipient. Indeed, several reports strongly suggest that a liver graft representing less than 0.8 per cent of the recipient's body-weight has a high risk of

early postoperative graft dysfunction³. As a consequence, adult-to-adult living transplantation programmes using right-side grafts have recently been initiated in some centres^{4,5}. Basically, the concept of using right-side grafts emerged from the good results observed in large series of patients undergoing extended liver resection for tumour associated with normal hepatic parenchyma. The analysis of these series has shown that, in experienced centres, the mortality and morbidity rates associated with such elective resections are about 0.5 and 10 per cent respectively⁶. However, the recent and rapid expansion of adult-to-adult right lobe donation in pioneering centres raises a number of concerns⁷.

The first concern is that whatever the results of living donor transplantation, for either children or adults, the procedure is one that potentially carries a 200 per cent mortality risk. Surprisingly, neither analysis of reported complications, nor the authors' own experience of 60 living donors (including 12 right lobe), has demonstrated any influence of the extent of liver resection on the operative risk⁸. In other words, if the surgical risk of left hepatectomy is low enough to be acceptable for living donation, there is no clear evidence that the risk of right hepatectomy might not be acceptable. Although the duration of the procedure is greater for right hepatectomy, the need for transfusion and the rate of biliary leak are similar for both procedures. Still, it is important to realize that, even if technical refinements prevent those complications directly related to major liver resection, complications indirectly related to surgery such as peptic ulcer and pulmonary embolism remain a major concern. 'Non-surgical' complications that are uncommon or perhaps underestimated after conventional liver resection may be more common in donors. We have observed, for example, a major pulmonary embolism in the early postoperative course of a 49-year-old man who gave his right lobe to his daughter; the patient had an uncommon coagulation disorder. This has led us to perform detailed investigations of haemostasis in all candidates for living donation to rule out those especially at risk of thrombotic complications.

A second concern is that, by moving from children to adult recipients, living related transplantation might increase the patient population significantly. Indeed, the number of adults who are currently waiting for a graft is

about ten times greater than that of children. As a result, more transplantation centres might be involved in living donation, including some insufficiently experienced in liver surgery and hepatology. It is likely that this would increase the donor morbidity rate to an unacceptable level and might also be a source of fatal events. To date, about 1000 cases of living donation have been reported. Although only one death has been described in the literature, two additional deaths have occurred⁷. A significant number of fatal events, even if concentrated in only a few centres, would obviously be unacceptable to the community as a whole.

A third concern is that, because of the scarcity of donors, efforts have been made to define guidelines aimed at determining which patients should be considered as potential transplant candidates. Those at especially high risk for transplantation, either because of the operative risk itself or because of the risk of rapid and deleterious disease recurrence, are currently not listed because the expected result of transplantation is too poor to justify the use of an organ that otherwise could have been used in a lower-risk patient. The extension of the pool of donors to healthy relatives would make such guidelines obsolete. It can be argued that the current guidelines have been established on the basis of organ shortage and that they would not necessarily be applicable to patients who have their own donor available. However, in the case of living donation, the extension of indications for transplantation to marginal recipients may have several deleterious consequences. First, it may further increase the number of centres involved in living related transplantation, including those with limited experience, thereby increasing the risks for donors. Second, the relatives of such marginal recipients may be faced with a difficult psychological dilemma as, in the absence of any alternative to living donation, they may be condemning the patient to die without a transplant. Third, psychological morbidity may be experienced by relatives who have participated in a palliative transplantation associated with a short life expectancy, such as that observed after transplanting patients with large or multiple hepatocellular carcinomas or cholangiocarcinomas for which the risk of recurrence with metastases after transplantation is very high within the early months⁹.

Finally, the issue of which degree of kinship should be considered as suitable for donation is far from being resolved. In order to prevent commerce in transplantation, living donation has been limited in several European countries to first-degree relatives, with the possibility of extension to spouses in cases of emergency¹⁰. In addition, in France, according to a 'bioethical law' introduced in 1994, the informed consent of the potential living donor has to be given to a judge or procurator, which gives additional protection against commercial transplantation.

Where are we going? There is no doubt that adult-to-adult living donor transplantation will be added to our armamentarium as a result of the enthusiastic reports of recent years. Therefore, the question is not whether adult-to-adult living donor transplantation will develop, but rather to what extent and in which way? The technique will probably be self-limiting to a significant degree as, after appropriate assessment, only 15–20 per cent of potential adult donors are suitable candidates. Indeed, the majority of potential donors are rejected because of ABO blood group incompatibility, major anatomical variations, psychosocial history and medical risk factors, such as obesity, steatosis or excessive alcohol intake. None the less, because many centres are now aware of the possibility of living related transplantation and wish to start performing such procedures, the medical community must establish a consensus view on such development. Consensus recommendations should be aimed at preventing serious and unacceptable ethical issues in relation to donors, as well as at ethical deviations in donation and the selection of transplant recipients.

Acknowledgements

The authors thank Professor James Garden of the University of Edinburgh for helpful assistance and comments.

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- 10 Cohen B, Persijn GG, Varenterghem Y Commerce in transplantation: how does it affect European legislation? *Clin Transpl* 2000; 14: 28-31.

On the editor's desk

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This article describes 'the moment of decision'.

So far this series has brought you from the reasons to write and from the first germ of an idea, through the difficulties and tribulations of writing, to the business of sending the final product for editorial assessment. The first section of this article deals with issues specific to the *British Journal of Surgery* and the second considers more general editorial matters.

An obvious place to begin is to ask: 'Who and what are editors?'. In the case of the *BJS*, editors are chosen and appointed by the British Journal of Surgery Society, a charity that is formally registered as a limited company, with audited accounts and statutory business meetings. No doubt preceding editors advise on suitable successors; the two current editors have worked up the ladder from referee, through associate editor, to their current position. The editors are not themselves members of the Council of the British Journal of Surgery Society; if this were the case, they would be in the awkward position of overseeing their own terms and conditions of service. It is observed that editors of other surgical journals frequently emerge from editorial boards.

The overall direction and strategy of the Journal comes from the Editorial Committee, almost as a mission statement: 'The *British Journal of Surgery* features the very best in clinical and laboratory-based research on all aspects of general surgery and related topics. Developing areas such as minimally invasive therapy and interventional radiology are strongly represented' (see Aims and scope, Journal frontispiece.) The editors are also involved in developments and innovations, such as new article formats and electronic mechanisms (website and article submission, referencing and publication, etc.). The bulk of an editor's work, however, is the day-to-day management of articles and letters received for consideration for publication.

The *BJS* editor's desk

Your article or letter will be read by at least one editor upon receipt. The immediate division is that reviews, leaders and vascular articles are dealt with by John Murie and the rest by John Farndon (editors). Articles may be sent to any of the

associate editors (Jonathan Earnshaw, Pierre Guillou and Ronan O'Connell) for a specialist opinion, or to Gordon Murray for statistical advice. They are then sent out to two or (usually) three referees. The number of articles rejected immediately at editorial level is about 5 per cent and comprises case reports (note: we do not seek these in our current state of excellent copy flow of high-quality articles) and articles that are inappropriate for the readership of the Journal (e.g. a new method of internal fixation of fractures of the fibula). Articles for immediate rejection are nearly always cross-checked between editors. No unsolicited article is accepted on editorial opinion alone.

If your article is one of the 95 per cent of papers that we receive (1200 to 1400 per year), read and send out to referees, we acknowledge receipt of your manuscript and choose referees to evaluate your work. This choice must be made carefully and objectively, and depends largely on the main theme of the article. Other clues that may help select suitable referees can be obtained from the bibliography, but care is needed to avoid sending an article submitted by Smidgin to be refereed by Buggins, when the article from Smidgin has discredited Buggins' life's work. The editors read almost 4000 reports each year from a panel of 1000 supportive *BJS* referees. We know who are hawks and who are doves. We know the degrees of concordance between our referees¹, and that the eventual outcome of the decision-making process is likely to be the same whether we choose the referees or you do². Referees provide a main report in free text plus a confidential report that relies greatly on objective scoring (Fig. 1). We place great store in this attempt at objectivity. A paper may obtain straight 'As' in importance of topic, analysis, presentation, etc., but it will be rejected if it has an 'E' for novelty. The decision to accept or reject is usually easy and is based on referee opinion; hanging judges are required from the Editorial Committee only rarely to reconcile widely differing reports. Difficult files are always discussed at the monthly meeting of the editors.

If a paper obtains marginal support, the editor will examine the manuscript once more, assess whether the criticisms are correctable, and will tend to err on the side of encouragement. Most articles are returned for corrections and for authors to attend to the referees' comments.

The British Journal of Surgery**Referee's Report Form****Confidential Comments for the Editors**

These are comments made in strict confidence to the *British Journal of Surgery* and will not be transmitted directly to the author(s), but may be used to aid revision of the manuscript.

This form is available for electronic submission from the *BJS* website (www.bjs.co.uk)

Reviewer's Details

Name

Email:

Date

Manuscript Details

Number

Title

Author(s)

Assessment

Please grade each feature (where appropriate) from A (excellent) to E (very poor)

	A	B	C	D	E
Novelty/originality	☐	☐	☐	☐	☐
Clinical importance	☐	☐	☐	☐	☐
Scientific importance	☐	☐	☐	☐	☐
Analysis of data	☐	☐	☐	☐	☐
Presentation/grammar/style (including illustrations, tables, etc.)	☐	☐	☐	☐	☐

Abstract

Does the summary give an adequate picture of the paper overall? Yes ☐ No ☐

Introduction

Are the aims and objectives of the paper set out *succinctly*? Yes ☐ No ☐

Are the aims and objectives of the paper set out *clearly*? Yes ☐ No ☐

Materials and methods

Are these clearly explained? Yes ☐ No ☐

Are the methods easily understood? Yes ☐ No ☐

Results

Are adequate numbers used? Yes ☐ No ☐

Is the statistical method appropriate? Yes ☐ No ☐

Are statistics necessary? Yes ☐ No ☐

Discussion and conclusions

Are the conclusions clearly stated? Yes ☐ No ☐

Are the conclusions justified? Yes ☐ No ☐

Are there any ethical issues to be addressed? Yes ☐ No ☐

Are the conclusions adequately discussed against the background of current and health issues? Yes ☐ No ☐

Recommendation

Please give an overall score to the paper where

- ☐ A - excellent, must publish
☐ B - good but needs minor correction
☐ C - correctable deficits, probably publish
☐ D - major faults ?reject
☐ E - very poor, reject outright

Additional Comments for the Editor

Please use this space to write any confidential comments to the Editor

Fig. 1 *British Journal of Surgery* referee's report form

Sometimes a hint of gloom will pervade the accompanying letter, 'You will see that our referees felt your article was seriously flawed', or a glimmer of hope will be provided, 'If you do resubmit your article...'

Errors of judgement in either direction occur infrequently. An article can end up on an associate editor's desk being prepared for publication after an editor and three referees have all failed to spot glaring errors. This usually occurs when the theme of an article is in the associate editor's specialty area. The initial decision to accept has to be reversed and the paper will be rejected with regrets and apologies. The Journal receives a challenge to its decision for less than 1 per cent of rejected articles. If the arguments presented by the authors requesting re-examination are cogent and objective, the paper may be reviewed again – usually by different referees who are not party to the past history of the paper.

The current acceptance rate of about 20 per cent reflects standards provided mainly by the referees. The editors have not adjusted the set point of acceptance–rejection in the last 5 years. With this strategy, and by concentrating on more substantial scientific papers, the citation index and impact factor of the Journal are rising. Once accepted, the editors work with authors to help polish the manuscript before typesetting. You may be asked to resubmit, attending further to points raised by referees and one or more editors. The resubmission will be checked again by an editor to ensure that referees' criticisms have been met and a final buff to high shine will be made to unify English, grammar, style and layout.

The editors hope that significant learning accrues even from rejected articles. Referees' comments are usually fed back to authors and these may help to re-craft the paper before submission to another journal. Hopefully, if the criticisms are profound the authors realize the need to do more work rather than attempt immediate resubmission. Although two or three referees' reports may be received, these are not all sent out to authors – a minority are of little use and some are too terse! Referees see reports from fellow referees specific for each article to provide bench-marking and hopefully to drive up the quality of the referee process.

The editor's desk cannot be tidy and effective without an efficient support team, and those in John Street are just such. We also meet regularly with our publisher, Blackwell Science, at away days in Oxford, exploring new methods and techniques to be implemented in editing and producing a journal of this century (see below).

The editor's desk in general

Editors want to receive high-quality papers that need minimal hands-on attention. Editors everywhere are aware

of the fragility of the peer review process and that: '(1) "Chiding" reviews to authors do not usefully improve quality. (2) Exchanging reviews has no effect on quality of review. (3) Reviewers aged 40 or less and those trained in epidemiology and statistics write better reviews. (4) Bias and parochialism can be found in most peer review systems and (5) Developing an instrument to measure manuscript quality remains the greatest challenge'³.

Internet peer review is an emerging editorial function that is acceptable to most authors and reviewers but this does not provide an adequate substitute for the commissioned prepublication review. Points in favour of prepublication internet review are that editors receive input from wide and unexpected sources and the internet system allows readers to gain some insight into the whole process⁴.

Editors must ensure that only work of high quality, with carefully described and tested methodology, is published. An article with poor methodology may produce skewed or erroneous end results and recommendations. Clinical practice may be affected by such a publication with serious consequences, or significant effects may be produced in a meta-analysis⁵.

Occasionally major pieces of work that have already been published are discredited. A recent example concerned a study of high-dose chemotherapy in patients with high-risk primary breast cancer (Bezwdoda and associates). Peer review and the editorial process was not an essential component of the conduct of the clinical work⁶ and editors must be forgiven for not spotting this type of fraud. This could have been prevented only by international registration of clinical trials with continuous monitoring of quality assurance⁷. In an attempt to improve the quality of research, some journals provide prospective advice on the structure and content of the proposed work before it begins, but without a definite commitment to publish any subsequent papers that may emanate from the work. Editors have a duty to declare openly any publishing misdemeanour detected within their domain and the *BMJ* has been pre-eminent in this activity. Professor Farthing writes later in this series on 'Ethics of publication'.

Editors must look forward and be ready to embrace new technology. In the future, will it be essential to have your work on four glossy pages of *BMJ* before anyone even begins to think about its credibility? Open internet peer review on the road to publication is one thing, but is the clinical scientific community ready for the e-print – a preliminary publication posted on a website that anyone can read and digest? E-print servers exist in some specialty areas, such as astronomy, and the *British Medical Journal* has recently posed the question: if you put up an article on a website, would this be publication?⁸. Would you want the work

endorsed later by paper publication? The *BMJ* has stated that the prior posting as an e-print would not preclude definitive paper publication: 'this is the age of transparency rather than paternalism' (Richard Smith, *BMJ* editor). The concept is developed further by Tony Delamothe (*BMJ* web editor) and Richard Smith⁹ who describe how 'their' journal, in partnership with Stanford University Libraries, will establish an e-print server. It is hoped that this will invigorate the review process, producing a higher quality end-product which could still be paper published. 'The e-print looks like the first substantially new form of scientific communication since the peer reviewed article, and as we're in the business of transmitting scientific information, it makes sense for us to work to find the e-print's right place in the new digital environment... We may find that we lose our jobs or have to accept reduced salaries if the BMJ Publishing Group becomes unprofitable because of proposals like that from the National Institutes of Health'⁹.

The editors of *BJS* are meeting with our current journal publishers during September and October to consider further the future of the electronic journal. We are pleased to be active in the process of change.

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Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement

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Background: The Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of clinical randomised controlled trials (RCTs).

Methods: The QUOROM group consisted of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers. In conference, the group was asked to identify items they thought should be included in a checklist of standards. Whenever possible, checklist items were guided by research evidence suggesting that failure to adhere to the item proposed could lead to biased results. A modified Delphi technique was used in assessing candidate items.

Findings: The conference resulted in the QUOROM statement, a checklist, and a flow diagram. The checklist describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. It is organised into 21 headings and subheadings regarding searches, selection, validity assessment, data abstraction, study characteristics, and quantitative data synthesis, and in the results with 'trial flow', study characteristics, and quantitative data synthesis; research documentation was identified for eight of the 18 items. The flow diagram provides information about both the numbers of RCTs identified, included, and excluded and the reasons for exclusion of trials.

Interpretation: We hope this report will generate further thought about ways to improve the quality of reports of meta-analyses of RCTs and that interested readers, reviewers, researchers, and editors will use the QUOROM statement and generate ideas for its improvement.

*Other members listed at end of paper

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Introduction

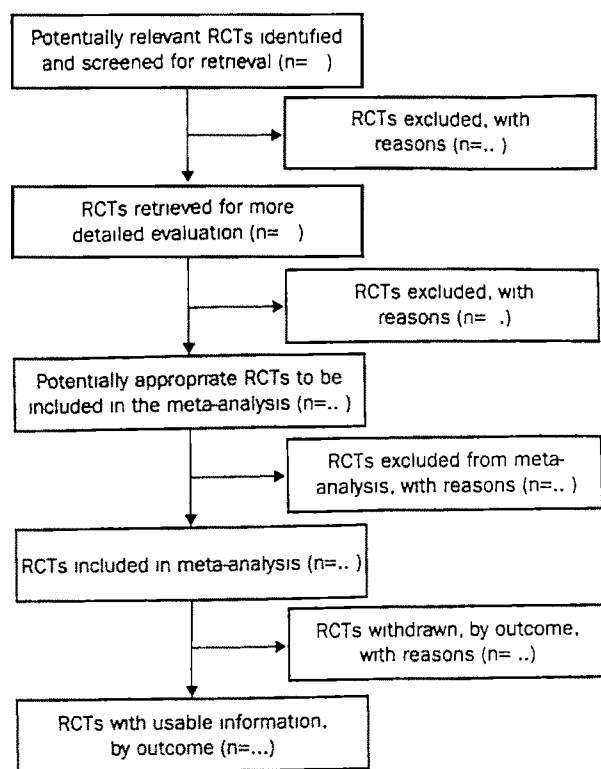
Health-care providers and other decision-makers now have, among their information resources, a form of clinical report called the meta-analysis¹⁻⁴, a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method³. The number of published meta-analyses has increased substantially in the past decade⁵. These integrative articles can be helpful for clinical decisions, and they may also serve as the policy foundation for evidence-based practice guidelines, economic evaluations, and future

research agendas. The value of meta-analysis is evident in the work of the international Cochrane Collaboration^{6,7}, the primary purpose of which is to generate and disseminate high-quality systematic reviews of health-care interventions.

Like any research enterprise, particularly one that is observational, the meta-analysis of evidence can be flawed. Accordingly, the process by which meta-analyses are carried out has undergone scrutiny. A 1987 survey of 86 English-language meta-analyses⁸ assessed each publication on 23 items from six content areas judged important in the conduct and reporting of a meta-analysis of randomised trials: study design, combinability, control of bias, statistical

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis [or systematic review] of RCTs ²⁶		
Abstract		Use a structured format ²⁷		
		Describe		
	Objectives	The clinical question explicitly		
	Data sources	The databases (i.e. list) and other information sources		
	Review methods	The selection criteria (i.e. population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and confidence intervals); and subgroup analyses		
	Conclusion	The main results		
Introduction		Describe		
		The explicit clinical problem, biological rationale for the intervention, and rationale for review		
Methods	Searching	The information sources, in detail ²⁸ (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status ²⁹ , language of publication ^{30,31})		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design ³²)		
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment, and their findings ³³⁻³⁸)		
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate) ^{35,36}		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c ³⁷ , and how clinical heterogeneity was assessed		
	Quantitative data synthesis	The principal measure of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed ³⁸ , a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias ³⁹		
Results	Trial flow	Provide a meta-analysis profile summarizing trial flow (see figure)		
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)		
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2 × 2 tables of counts, means and SDs, proportions)		
Discussion		Summarize key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda		

Quality of reporting of meta-analyses



Progress through the stages of a meta-analysis for RCTs

analysis, sensitivity analysis, and problems of applicability. The survey results showed that only 24 (28%) of the 86 meta-analyses reported that all six content areas had been addressed. The updated survey, which included more recently published meta-analyses, showed little improvement in the rigour with which they were reported⁹.

Several publications have described the science of reviewing research¹, differences among narrative reviews, systematic reviews, and meta-analyses², and how to carry out^{3,4,10}, critically appraise^{11–15}, and apply¹⁶ meta-analyses in practice. The increase in the number of meta-analyses published has highlighted such issues as discordant meta-analyses on the same topic¹⁷ and discordant meta-analyses and randomised-trial results on the same question¹⁸.

An important consideration in interpretation and use of meta-analyses is to ascertain that the investigators who did the meta-analysis not only report explicitly the methods they used to analyse the articles they reviewed, but also report the methods used in the research articles they analysed. The meta-analytical review methods used may not be provided when a paper is initially submitted: even when they are, other factors such as page limitations, peer review,

and editorial decisions may change the content and format of the report before publication.

Several investigators have suggested guidelines for reporting of meta-analyses^{3,19}. However, a consensus across disciplines has not developed. After the initiative to improve the quality of reporting of randomised controlled trials (RCTs)^{20–22}, we organized the Quality of Reporting of Meta-analyses (QUOROM) conference to address these issues as they relate to meta-analyses of RCTs. This report summarises the proceedings of that conference. The issues discussed might also be useful for reporting of systematic reviews (i.e. meta-analysis, as defined above, without statistical aggregation), particularly of RCTs.

Methods

The QUOROM steering committee began with a comprehensive review of publications on the conduct and reporting of meta-analyses. The databases searched included MEDLINE and the Cochrane Library²³, which consists of the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the York Database of Abstracts of Reviews of Effectiveness, and the Cochrane Review Methodology Database. We examined reference lists of the retrieved articles and individual personal files. Articles of potential relevance were retrieved and critically appraised by the QUOROM steering committee. The committee generated a draft agenda for the conference, which included six domains requiring discussion and debate. The content areas were slightly modified during preliminary discussions at the conference and are reported as: the search for the evidence; decision-making on which evidence to include; description of the characteristics of primary studies; quantitative data synthesis; reliability and issues related to internal validity (or quality); and clinical implications related to external validity (or generalisability).

In planning the QUOROM conference, the steering committee identified clinical epidemiologists, clinicians, statisticians, and researchers who conduct meta-analysis as well as editors from the UK and North America who are interested in meta-analysis. These 30 individuals were invited to a conference in Chicago on Oct 2–3, 1996. Participants were surveyed before the meeting to elicit their views on current reporting standards of meta-analyses and whether these needed improvement. In addition, they were sent relevant citations for review and were asked to indicate in which of the six groups they wished to participate.

The conference included small-group and plenary sessions. Each small group had a facilitator who was a member of the steering committee and was responsible for ensuring the discussions of as many as possible of the issues relevant to their specific remit. Each small group also had a

recorder, who was responsible for documenting the main points and the consensus on each issue discussed during that session; the recorder presented the group's consensus during the plenary sessions. During the plenary sessions, an elected scribe from each small group was responsible for recording the principal points relevant to that group's charge that arose during the plenary discussion.

The participants in each small group were asked to identify items that they thought should be included in a checklist of standards that would be useful for investigators, editors, and peer reviewers. We asked that, whenever possible, items included in the checklist be guided by research evidence that suggested that a failure to adhere to the particular checklist item proposed could lead to biased results. For example, a substantial lack of sensitivity and specificity of MEDLINE searches is evident²⁴. Therefore, the checklist suggests that investigators explicitly describe all search strategies used to locate articles for inclusion in a meta-analysis. In considering whether candidate items were essential, each subgroup used a modified Delphi technique²⁵ that was replicated in the plenary sessions.

Results

The conference resulted in the QUOROM statement: a checklist (table) and a flow diagram (figure). The checklist of standards for reporting of meta-analyses describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. The checklist is organized into 21 headings and subheadings to encourage authors to provide readers with information on searches, selection, validity assessment, data abstraction, study characteristics, quantitative data synthesis, and trial flow. Authors are asked to provide a flow diagram (figure) providing information about the number of RCTs identified, included, and excluded and the reasons for excluding them¹⁰.

Pretesting

After development of the checklist and flow diagram, two members of the steering committee (DM, DJC) undertook pretesting with epidemiology graduate students studying meta-analysis, residents in general internal medicine, participants at a Canadian Cochrane Center workshop, and faculty members of departments of medicine and of epidemiology and biostatistics. One group of candidates for a master's degree in epidemiology used the checklist and flow diagram to report their meta-analyses as if their work were being submitted for publication. Feedback from these four groups was positive, most users stating that the checklist and flow diagram would be likely to improve

reporting standards. Modifications of the checklist (e.g. inclusion of a statement about major findings) and changes to the flow diagram (e.g. more detail) were incorporated.

Discussion

In developing the checklist, we identified supporting scientific evidence for only eight of 18 items to guide the reporting of meta-analyses of RCTs²⁶⁻³⁹. Some of this evidence is indirect. For example, we ask authors to use a structured abstract format. The supporting evidence for this item was collected by examining abstracts of original reports of individual studies²⁷ and may not pertain specifically to the reporting of meta-analyses. However, the QUOROM group judged this a reasonable approach by analogy with other types of research reports and pending further evidence about the merits of structured abstracts for meta-analyses.

We have asked authors to be explicit in reporting the criteria used when assessing the 'quality' of trials included in meta-analyses and the outcome of the quality assessment. There is direct and compelling evidence to support recommendations about reporting on the quality of RCTs included in a meta-analysis. A meta-analytic database of 255 obstetric RCTs provided evidence that trials with inadequate reporting of allocation concealment (i.e. keeping the intervention assignments hidden from all participants in the trial until the point of allocation) overestimated the intervention effect by 30% compared with trials in which this information was adequately reported³³. Similar results for several disease categories and methods of quality assessment have been reported³⁴. These findings suggest that inclusion of reports of low-quality RCTs in meta-analyses is likely to alter the summary measures of the intervention effect.

We also ask authors to be explicit in reporting assessment of publication bias, and we recommend that the discussion should include comments about whether the results obtained may have been influenced by such bias. Publication bias derives from the selective publishing of studies with statistically significant or directionally positive results⁴⁰⁻⁴², and it can lead to inflated estimates of efficacy in meta-analyses. For example, trials of single alkylating agents versus multiple-agent cytotoxic chemotherapy in the treatment of ovarian cancer have been analysed³⁹. Published trials yielded significant results in favour of the multiple-agent therapy, but that finding was not supported when the results of all trials – both those published and those registered but not published – were analysed.

The statement asks authors to be explicit about the publication status of reports included in a meta-analysis. Only about a third of published meta-analyses report the

inclusion of unpublished data^{29,43}. Although one study found that there were no substantial differences in the dimensions of study quality between published and unpublished clinical research⁴², another suggested that intervention effects reported in journals were 33% greater than those reported in doctoral dissertations⁴⁴. The role of the 'grey literature' (difficult to locate or retrieve) was examined in 39 meta-analyses that included 467 RCTs, 102 of which were grey literature²⁹. Meta-analyses limited to published trials, compared with those that included both published and grey literature, overestimated the treatment effect by an average of 12%. There is still debate between editors and investigators about the importance of including unpublished data in a meta-analysis⁴³.

We have asked authors to be explicit in reporting whether they have used any restrictions on language of publication. Roughly a third of published meta-analyses have some language restrictions as part of the eligibility criteria for including individual trials³⁰. The reason for such restrictions is not clear, since there is no evidence to support differences in study quality, and there is evidence that language restrictions may result in a biased summary. The reports of 127 RCTs written in English, compared with those reported in four other languages, showed little or no difference in several important methodological features⁴⁵. Similar results have been reported elsewhere³¹. The role of language restrictions has been studied in 211 RCTs included in 18 meta-analyses in which trials published in languages other than English were included in the quantitative summary³⁰. Language-restricted meta-analyses overestimated the treatment effect by only 2% on average compared with language-inclusive meta-analyses. However, the language-inclusive meta-analyses were more precise³⁰.

Reports of RCTs with statistically positive results are more likely than those with negative results to be published in English³¹. Likewise, there is emerging evidence to suggest that reports of RCTs from certain countries mostly have statistically positive results⁴⁶.

We used several methods to generate the checklist and flow diagram: a systematic review of the reporting of meta-analyses; focus groups of the steering committee; and a modified Delphi approach during the conference. Although we did not involve certain users of meta-analyses (policy-makers or patients), we formally pretested this document with representatives of several constituencies who would use the recommendations and made modifications accordingly.

The QUOROM group also discussed the format of a meta-analysis report, how best to assess the impact of the QUOROM statement, and how best to disseminate it. The format we recommend includes 15 subheadings that reflect

the sequential stages in the conduct of the meta-analysis within the text of the report of a meta-analysis. The checklist included in the statement can also be used during the planning, performing, and reporting of a meta-analysis and during peer review of the report after its submission to a journal.

We delayed publication of the QUOROM statement until its impact on the editorial process had been assessed. We organized an RCT involving eight medical journals to assess the impact of use of QUOROM criteria on journal peer review. Accrual is now complete and we will report the trial results elsewhere.

After about 5 weeks of electronic posting we had received five comments from investigators, whom we thank for their thoughtful consideration of the statement. Several issues, in particular in relation to terminology, cannot be addressed in the statement at present. The QUOROM group is agreed on the importance of making changes to the checklist in the light of documented evidence and must resist changes based on opinion or anecdotal evidence unless there is a compelling rationale for doing otherwise. Nonetheless, the issues raised have been noted for consideration and discussion in future.

Several queries addressed the distinction between the meta-analysis and systematic review. As we indicate in the introduction, and throughout the statement, the QUOROM group agreed to observe the distinction as defined by the Potsdam consultation on meta-analysis³.

We were also asked to clarify the checklist item asking investigators to interpret their results in light of the totality of evidence. Increasingly, several meta-analyses on the same topic are reported⁴⁷⁻⁴⁹. If other similar reports are available, authors should discuss their results as they relate to such evidence.

For the QUOROM statement to continue to be useful, it must remain evidence based and up to date. Members of the QUOROM group need to survey the literature continually to help inform themselves about emerging evidence on reporting of meta-analyses. This information needs to be collated and presented annually for two purposes. The first is decisions on which checklist items to keep, delete, or add; these decisions can be made similarly to the selection of the original items. The second purpose is so that an up to date summary on the reporting of meta-analyses can be prepared. These efforts are being coordinated through a website. This approach is similar to the CONSORT initiative.

In summary, our choice of items to include in a meta-analysis report was based on evidence whenever possible, which implies the need to include items that can systematically influence estimates of treatment effects. Currently, we lack a detailed understanding of all the factors leading to

bias in the result of a meta-analysis. Clearly, research is required to help improve the quality of reporting of meta-analyses. Such evidence may also act as a catalyst for improving the methods by which meta-analyses are conducted.

The QUOROM checklist and flow diagram are available on *The Lancet's* website [http://www.thelancet.com]. We hope that this document will generate further interest in the field of meta-analysis and that, like the CONSORT initiative, the QUOROM statement will become available in different languages and locations as it is disseminated. We invite interested readers, reviewers, researchers, and editors to use the QUOROM statement and generate ideas for improvement.

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Contributors

David Moher, Deborah Cook, Susan Eastwood, Ingram Olkin, Drummond Rennie, and Donna Stroup developed the QUOROM statement. They all planned the meeting, participated in regular conference calls, identified and secured funding, identified and invited participants, and planned the meeting agenda. All of them helped write the report, including revisions.

QUOROM participants

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Immediate breast reconstruction after mastectomy for cancer

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Background: Immediate breast reconstruction after mastectomy has increased over the past decade following the unequivocal demonstration of its oncological safety and the availability of reliable methods of reconstruction. Broadly, it is undertaken in the treatment of breast cancer, after prophylactic mastectomy in high-risk patients, and in the management of treatment failure after breast-conserving surgery and radiotherapy. Immediate breast reconstruction can be achieved reliably with a variety of autogenous tissue techniques or prosthetic devices. Careful discussion and evaluation remain vital in choosing the correct technique for the individual patient.

Methods: This review is based primarily on an English language Medline search with secondary references obtained from key articles.

Results and conclusion: Immediate breast reconstruction is a safe and acceptable procedure after mastectomy for cancer; there is no evidence that it has untoward oncological consequences. In the appropriate patient it can be achieved effectively with either prosthetic or autogenous tissue reconstruction. Patient selection is important in order to optimize results, minimize complications and improve quality of life, while simultaneously treating the malignancy. Close cooperation and collaboration between the oncological breast and reconstructive surgeons is desirable in order to achieve these objectives.

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Introduction

In the UK, breast cancer is the commonest malignancy in women with around 26 000 new cases diagnosed annually¹. About 40 per cent of these patients require mastectomy because of diffuse multifocal disease, tumour size or site, concern about the desirability of radiotherapy, or merely strong patient preference for mastectomy. Additionally, a number of women initially undergoing breast-conserving surgery later have a mastectomy because of incomplete resection margins or local recurrence. Breast reconstruction may, therefore, be required in a significant proportion of all patients with breast cancer. Breast reconstruction after mastectomy has become popular over the past 20 years for several reasons. The evolution of safe and predictable reconstructive techniques has been coupled with an increased availability of plastic surgical expertise. Simultaneously, there has been heightened patient awareness of, and demand for, the various reconstructive options, and widespread recognition by surgeons and oncologists of the psychological benefits of reconstruction.

Historically, almost all breast reconstructions were delayed for months or years after mastectomy. It was feared that immediate breast reconstruction would compromise adjuvant treatment and that such therapy would increase the risk of postoperative complications. There was further concern that it would mask locoregional recurrence and render treatment of such disease difficult. However, there are several obvious benefits such as the potential for a single operation and period of hospitalization, better psychological adjustment to the loss of the breast, and better aesthetic results. Drawbacks include the increased length of procedure, difficult logistics (between ablative and reconstructive surgeons) and more complex surgery.

Not all candidates are suitable for immediate breast reconstruction, for instance those with significant cardiopulmonary or other systemic disease. The surgical risk factors for individual operations, for example the transverse rectus abdominis myocutaneous (TRAM) flap, are well understood and include chronic obstructive airway disease, severe cardiovascular disease, uncontrolled hypertension, morbid obesity, insulin-dependent diabetes mellitus and

general debility. Oncologically, patients with diffuse metastatic disease are not candidates for breast reconstruction, but those with locally advanced or aggressive cancers may undergo successful reconstruction.

This article reviews the literature on immediate breast reconstruction after mastectomy and provides a pragmatic approach for the oncological breast and reconstructive surgeon.

Techniques of immediate reconstruction

Modern breast reconstruction techniques have evolved steadily since the introduction of the silicone gel-filled implant in the early 1960s. Today they comprise the use of prosthetic materials, autogenous tissue or a combination of the two. Because of the variable needs of individual patients, the reconstructive surgeon must be able to provide all options to patients². In general the aesthetic results from autogenous tissue reconstruction are superior to those of prosthetic reconstruction^{3,4}. The latter may involve a simple breast implant, a tissue expander followed by an implant, a permanent expander-implant or an adjustable prosthesis⁵⁻¹⁶. Autogenous tissue for immediate breast reconstruction can be supplied by the TRAM flap, latissimus dorsi (LD) myocutaneous flap, inferior and superior gluteal flaps, and the lateral transverse thigh flap¹⁷⁻²⁵. Prostheses and autogenous tissue are not mutually exclusive, however, and expanders or implants are often used in combination with LD flaps²⁶, or occasionally with TRAM flaps^{27,28}.

Prosthetic reconstruction (Figs 1-5)

Implant reconstruction

Primary implant reconstruction was commonly performed in the 1980s but its popularity has waned. Today its role is limited to patients with small volume requirement (A/B cup size or volume below 400 ml) who have adequate soft tissue coverage, especially skin. This stringent requirement occurs most often in delayed reconstruction or immediate reconstruction with short healthy skin flaps or with the aid of a LD flap. The ideal patient is a young non-smoker with good chest wall musculature²⁹.

Notwithstanding the above, the insertion of a gel- or saline-filled prosthesis under the pectoralis major-serratus anterior musculofascial complex is undoubtedly the simplest method of immediate reconstruction. The placement of a gel-filled prosthesis subcutaneously under mastectomy flaps^{6,7,30} should be of only historical interest because of the high incidence of flap necrosis, wound dehiscence, implant extrusion, infection and peri-implant capsular contrac-

ture^{31,32}. In contrast, the submuscular position³³⁻³⁵ protects against exposure, malposition and capsular contracture^{5,33,36-38}; a direct comparison of subcutaneous and submuscular implants has demonstrated the superiority of the subpectoral position³¹. Furthermore, implants deep to muscle theoretically minimize the possibility of the device masking recurrent disease³⁹. Total muscular coverage may not, however, prevent implant loss entirely, and may result in poorer projection of the reconstructed breast⁴⁰⁻⁴².

The commonest and least predictable complication of breast implant surgery is capsular contracture^{35,43,44}. Submuscular placement of silicone gel-filled implants consistently decreases the incidence of significant contracture from 60 to 30 per cent^{31,45-49}, although this often may be confounded by the effect of preoperative or postoperative irradiation⁴⁷⁻⁴⁹. It has also been demonstrated unequivocally that the use of saline-filled rather than silicone gel-filled implants decreases the incidence of contracture without reducing the degree of patient satisfaction with the procedure^{37,38,50}. Similarly, in retrospective and prospective trials of breast augmentation, textured-surface prostheses have been shown significantly to diminish the incidence of adverse capsule formation to around 10 per cent or less⁵¹⁻⁵⁴. Implant surface texturing by inducing tissue adherence also decreases the risk of malposition of breast prostheses⁵⁵. Finally, in addition to capsular contracture, a common problem with implant reconstruction is the presence of palpable and sometimes visible ripples, especially in slim women.

Patients with silicone gel implants do not appear to be oncologically disadvantaged. In a study of 146 women, who had undergone breast reconstruction with silicone gel-filled implants after mastectomy, the risks of distant metastasis and breast cancer-related death were actually lower than in matched controls. Furthermore, reconstruction did not significantly increase the risk of local recurrence, second breast cancer or second primary tumour at another site⁵⁶.

Classical expander-implant reconstruction

Breast reconstruction by tissue expansion was pioneered by Radovan⁸. In its classical form it entails the submuscular placement of an inflatable silicone balloon which is subsequently expanded by a series of postoperative saline injections through a remote port to create a breast mound of the desired dimensions; this takes several weeks^{9,57}. The temporary expander is then removed at a second stage (4-6 months later) and replaced with a permanent implant.

The main advantage of tissue expander reconstruction is the use of local tissues with similar colour, texture and subcutaneous tissues to the surrounding chest wall. Initially,

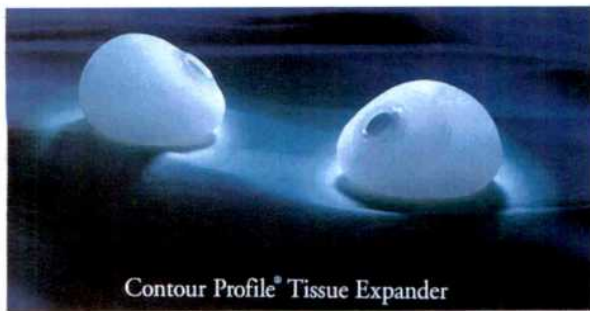


Fig. 1 Mentor Contour Profile anatomical tissue expander with integrated valve



Fig. 2 McGhan anatomical expandable implant style 150 with permanent remote fill tube and injection port



Fig. 3 Mentor Siltex Becker 50 expander-implant with fill tube and injection port

delayed placement of the tissue expander was preferred in an attempt to decrease local complications^{58,59}, but immediate tissue expander reconstruction after mastectomy is now well established^{4,11–15}. The ideal candidates for immediate reconstruction are those with smaller, minimally ptotic breasts, and those having immediate bilateral reconstruction when radiotherapy is not anticipated. Following placement of the expander in the submuscular pocket at the time of mastectomy, expansion is carried out at intervals of 1 week on an outpatient basis. The volume at which the breast mound looks equal to the contralateral breast is noted (to guide the choice of size of the permanent implant). The expander is then overinflated to about 150–200 per cent of the desired final breast volume^{12,57,60,61}. Subsequent volume reduction results in a more naturally shaped breast^{10,16,59}, and may result in a lower incidence of capsular contraction⁵⁷.

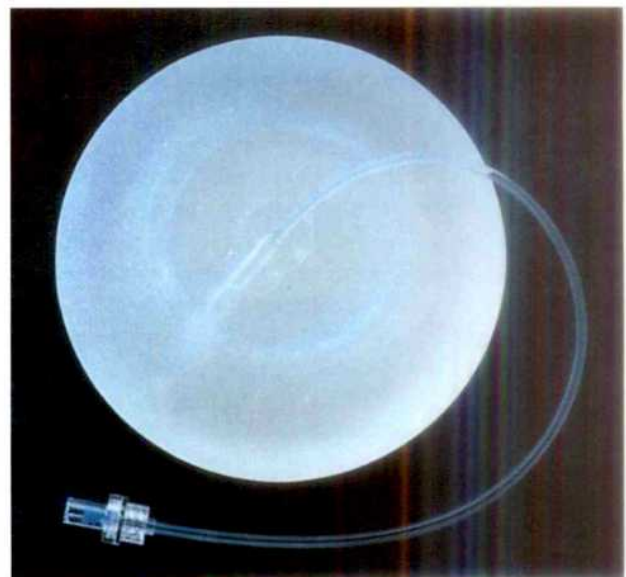


Fig. 4 Mentor Spectrum postoperatively adjustable expander-implant with fill tube

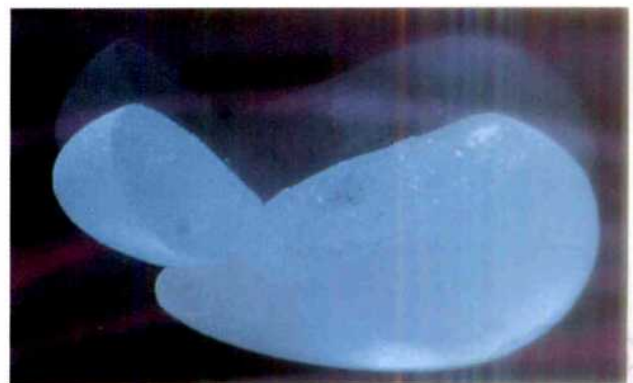


Fig. 5 McGhan anatomical cohesive gel breast implant demonstrating the semisolid gel

Although completion of expansion usually takes 6–8 weeks, expander-to-implant exchange is usually delayed for some months after achieving the desired size. This delay may not be necessary as Foo *et al.*⁶², in a prospective randomized controlled trial comparing the insertion of the definitive prosthesis at 2 weeks and 6 months after completion of expansion, found no difference in adverse capsular contracture rates (24 *versus* 26 per cent). To achieve maximum symmetry in tissue expander reconstruction may require significant alteration of the contralateral breast by mastopexy, reduction or augmentation. Nipple-areolar reconstruction is also usually undertaken at this second stage. In summary, the indications for immediate breast reconstruction by tissue expansion include: (a) patients with small volume requirements (small, preferably non-ptotic breasts); (b) patients who have not been irradiated previously or in whom no postoperative radiotherapy is anticipated; (c) bilateral reconstructions as it is easy to achieve symmetry with any technique; and (d) patients who are unfit or unwilling to undergo major surgical procedures for reconstruction.

The main advantages of breast reconstruction by tissue expansion are its simplicity, and shorter operating, hospitalization and recovery times. The main drawbacks are difficulty in achieving ptosis^{42,63}, projection in the nipple area, lack of natural consistency especially with saline implants, and an almost 30 per cent incidence of adverse capsular contracture^{16,60,62,64,65}. The incidence of capsular contracture has, however, been dramatically decreased with the use of textured-surface expanders^{55,66,67} and implants^{53,54}. Breast implant rupture with time, common in second-generation gel prostheses⁶⁸, is not a major issue with the new-generation implants.

The most devastating complication of tissue expander breast reconstruction is exposure and extrusion of the prosthesis which inevitably leads to a failed reconstruction. Historically, the reported rates of implant loss were as high as 30–50 per cent^{11,12,16,29,40,41,45,69,70}. It results from wound dehiscence secondary to mastectomy skin flap necrosis, infection, erosion of the overlying skin and tissues by a fold in the expander, poor soft tissue coverage, and expanding irradiated tissue⁴⁷. The recent advances that have simplified breast reconstruction by tissue expansion and made it more predictable are the use of textured-surface^{55,66,67} and anatomical breast-shaped expanders with integrated injection ports^{11,71–74}.

Adjustable implant reconstruction

In order to avoid the need for a second stage in expander-implant reconstruction, permanent expander-implants were developed^{14,16,61}. The Becker expander/mammary

prosthesis (Mentor Medical Systems, Wantage, Oxford, UK) and the McGhan style 150 expandable breast implant (Inner Medical, Wokingham, UK) have an adjustable saline-filled inner lumen surrounded by a silicone gel outer lumen (25–50 per cent of the nominal implant size). The gel renders the implants more natural-feeling while the saline compartment allows volume adjustment. More recently Mentor Medical Systems has developed the Spectrum postoperatively adjustable prosthesis which is entirely saline filled (i.e. with no gel component) and is being used increasingly in the USA. The indications for adjustable implant reconstruction are similar to those for simple prosthetic reconstruction. The ideal candidates are those with: (a) anticipated or actual skin deficiency at mastectomy which precludes simple implant reconstruction; (b) contralateral ptosis that cannot be matched with a simple permanent implant (the overexpansion followed by deflation to the ideal volume achieves a good cosmetic result); and (c) large chest wall diameters with moderate obesity and hypertrophy or ptosis not severe enough to warrant mastopexy or breast reduction.

Autogenous tissue reconstruction

Immediate reconstruction using autologous tissue yields the most durable and natural-appearing results with the greatest consistency⁷⁵. It has several general advantages.

- 1 A large volume of the patient's own tissue is available.
- 2 No prosthesis is required, obviating problems such as infection, extrusion, malposition and capsular contracture.
- 3 It is suitable for patients who do not want implants.
- 4 It offers unrivalled versatility, including creation of excellent ptosis and fill of the infraclavicular hollow and anterior axillary fold.
- 5 These tissues can withstand postoperative radiotherapy and can also be used in previously irradiated patients undergoing completion mastectomy for recurrence.
- 6 The excellent vascularity of the tissues leads to improved wound healing.

The autogenous tissues available in decreasing order of frequency of use are the TRAM, LD, superior gluteal, inferior gluteal, lateral transverse thigh and Taylor–Rubens peri-iliac flaps.

Transverse rectus abdominis myocutaneous flap (Fig. 6)

The TRAM flap, the most widely used autogenous tissue, was first described by Hartrampf *et al.*¹⁸ in 1982 in Atlanta.

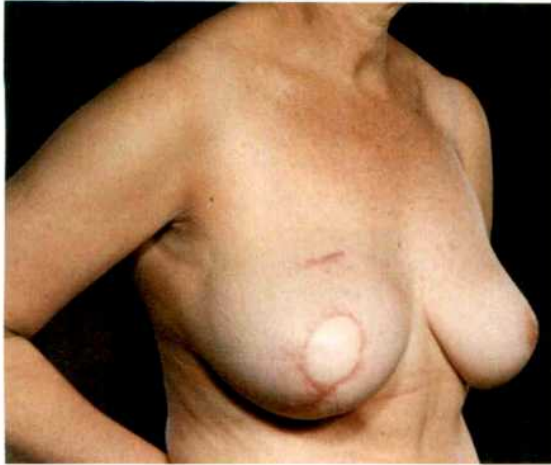


Fig. 6 Cosmetic result of immediate breast reconstruction with pedicled transverse rectus abdominis myocutaneous flap

Conventionally, it relies on the blood flow through the deep superior epigastric pedicle within the rectus abdominis muscles to supply a horizontal ellipse of overlying abdominal wall skin and fat. The TRAM flap can be raised either as a conventional pedicled flap (based on the deep superior epigastric vessels) or as a microvascular free flap (based on the larger deep inferior epigastric vessels). Pedicled TRAM flaps can be ipsilateral or contralateral, unipedicled or bipedicled, unilateral or bilateral, surgically delayed or immediate. Free TRAM flaps can utilize the full width of the muscle^{19,76}, be partial muscle sparing^{77,78} or, more recently, be total muscle-sparing perforator flaps^{79–84}.

The TRAM flap has become established as the 'gold standard' for breast reconstruction^{75,85}. It gives the most natural-appearing breast with the most natural feel, and is associated with the fewest complications compared with all other reconstructive techniques^{4,86}. It also has excellent reliability and donor site cosmesis and so may be used preferentially unless there are compelling reasons not to do so. Its specific advantages are: (a) availability of a large volume of well vascularized autogenous tissue; (b) ability to withstand postoperative radiotherapy; (c) utility in sites of previous irradiation or tight chest wall skin; (d) good ptosis (versatility in balancing the opposite breast even in the presence of ptosis or a large contralateral breast); and (e) concomitant beneficial reduction of excess abdominal tissue ('tummy tuck') and the highly favourable donor site scar.

Contraindications include patients who do not want or cannot withstand a major operation, elderly patients, and the lack of adequate tissue from the abdomen such that implants are needed. Adverse risk factors include weight more than 25 per cent over the ideal, smoking, diabetes mellitus, autoimmune disease, psychological problems,

abdominal scars and an inexperienced surgeon⁸⁷. Disadvantages of the TRAM flap include: (a) a major operation 'requiring exacting training and technique of the surgeon'¹⁷; (b) a longer operation (3–8 h depending on the variant) and longer hospital stay (5–10 days) compared with prosthetic or other reconstructions³; (c) risk of partial or total flap loss; (d) increased possibility of blood transfusion³; (e) risk of abdominal wall hernia and bulges; (f) frequent need for prosthetic mesh reinforcement of the abdominal wall; (g) a long transverse abdominal scar; and (h) increased general complications of major surgery such as deep vein thrombosis, pneumonia and adult respiratory distress syndrome⁸⁷.

Significant complications may occur with the TRAM flap⁸⁷ and their incidence is increased dramatically by obesity^{66,88}, especially if more than 25 per cent above the ideal body-weight, smoking⁸⁹, underlying systemic disease (diabetes, collagen vascular disease, hypertension), previous abdominal surgery and scars, and prior irradiation^{87,90}.

There are a number of options in TRAM flap technique designed to maximize its success and consistency while minimizing morbidity^{91,92}. The two main variants are the conventional (pedicled) and the free flap, with the latter relying on microvascular tissue transfer. In general, the free flap is preferred to the pedicled variant because of its reduced risk of localized fat necrosis and partial flap loss, owing to its more reliable blood supply^{77,93}.

Single-pedicled TRAM flap

This is indicated in patients who are non-smokers, not obese, with no peripheral vascular disease or diabetes mellitus. It is generally reserved for those aged below 60 years and, ideally, with a small-to-moderate volume requirement. It is also a good choice for bilateral reconstruction when a hemi-TRAM flap is used for each side.

Double-pedicled TRAM flap^{91,94}

The use of two rectus muscle pedicles increases the blood flow to the overlying skin and fat, thereby increasing the reliability and size of the flap. Its indications are limited because of the morbidity associated with abdominal wall damage and the effect on cardiorespiratory function. Because of its effect on the abdominal wall, young women are unsuitable for this procedure; it is also better avoided in the elderly because of compromise of respiratory function. It is used primarily to augment the circulation in obese patients, smokers, diabetics, and in those with peripheral vascular disease, chest wall irradiation and other microvascular risk factors. It is especially useful for patients in

whom a large amount of tissue is needed on the chest wall⁹¹, for example those with previous irradiation, inflammatory carcinoma, chest wall spread or recurrence. It is also useful in patients with midline scars from previous surgery. It is very controversial, however, with some claiming that it amounts to medical malpractice to use such a flap⁹⁵ and others justifying it on grounds of reliability^{74,87,94}.

Conventional TRAM flap with preoperative surgical delay

In the surgically delayed TRAM flap, the dominant deep inferior epigastric pedicle is ligated or divided, thus increasing the blood flow through the deep superior epigastric vessels^{96,97}. This has the effect of increasing the viable dimensions of the pedicled flap, and decreasing flap necrosis in the high-risk patient. It also decreases the need for double-pedicled TRAM flaps and reduces venous congestion within the flap⁹⁸. It is indicated in high-risk patients who do not want a free flap, or when the reconstructive surgeon has no microsurgical skill or equipment. Specific indications for preoperative TRAM flap delay are: (a) smoker; (b) greater than 20 per cent of ideal body-weight (obese patients with abdominal pannus); (c) history of chest wall irradiation; (d) diabetes mellitus; (e) hypertension or cardiovascular disease; (f) patients with high volume requirements; and (g) autoimmune disease.

Although it is a simple and effective technique, it nevertheless carries some morbidity. It is often associated with asymptomatic localized seromas; infection, dehiscence and hernia are rare. The standard technique involves ligation and division of the ipsilateral deep and superficial inferior epigastric vessels^{96,97}. Sometimes the deep inferior and superior epigastric vessels on both sides are divided either through two separate incisions or one extended suprapubic incision. Classically this is undertaken 2–3 weeks before flap elevation, although 3 days may be all that is really needed to increase viability and reliability.

Mid-abdominal TRAM flap

In this variant, the horizontal location of the abdominal ellipse is moved up towards the mid or even upper abdomen in order to increase the blood flow to the overlying skin and fat⁹⁹. It exploits the concentration of the musculocutaneous perforating vessels in the periumbilical region⁹⁶ and the location of the choke vessels just above the umbilicus^{97,100}. It has not achieved widespread use, perhaps because of the highly visible scar and the availability of other reliable TRAM flap variants. The mid-abdominal TRAM flap may avoid fascial closure below the umbilicus and so decrease the risk of weakness of the abdominal wall.

'Supercharged' pedicled TRAM flap

This involves reconnection of the opposite deep or superficial inferior epigastric vessels by microvascular anastomoses to recipient vessels in the axilla, while maintaining the other pedicle based superiorly^{2,101,102}. Its main use is to rescue 'struggling' flaps, especially those with venous congestion as sometimes occurs in borderline high-risk patients undergoing immediate conventional TRAM flap reconstruction.

'Turbocharged' pedicled TRAM flap

In this variant the two deep inferior epigastric vessels are joined to each other by microvascular anastomosis as a loop to increase the circulation to the side contralateral to the pedicle¹⁰³. Its main use is to augment the blood flow of single-pedicled TRAM flaps in patients with lower midline abdominal scars.

Free TRAM flap

First described in 1979 by Holmstrom¹⁹, the inferiorly based free TRAM flap relies on the more robust deep inferior epigastric vessels⁹⁶. It thus has better vascularity and less risk of ischaemia to its peripheral zones (and consequently less fat necrosis and partial flap loss)^{77,93,104–106} than the pedicled TRAM flap. It is the preferred TRAM flap technique in many centres^{77,105–108}.

This flap reliably carries a larger amount of skin and subcutaneous fat than the conventional TRAM flap. It is therefore desirable when large volumes of tissue are required and delay or bipedicled techniques are not feasible or desirable. It is the TRAM flap of choice in patients with risk factors (obesity, smoking, diabetes, peripheral vascular, autoimmune, and cardiovascular disease), and is ideal for those who have abdominal scars, especially upper abdominal scars. Its drawbacks are added theatre time, increased difficulty in performance and the possibility of total flap failure. The chances of total flap failure are 5–6 per cent, with a re-exploration rate of 10–15 per cent^{107,108}. With increasing experience of the operating team, these values should decrease to 1 and 3 per cent respectively^{105,109}. Although one of its key indications is cigarette smoking, patients who smoke have an increased risk of partial flap and fat necrosis, pneumonia and atelectasis. Ideally they should stop smoking several weeks before surgery and for 6 weeks thereafter. However, to avoid delay in cancer treatment, immediate free TRAM flap breast reconstruction is routinely undertaken even in those who continue to smoke up to the day of operation.

Free TRAM flaps may be used for both unilateral and bilateral reconstructions, and the former may be ipsilateral or contralateral. In immediate reconstruction, the choice of which side to base the vessels on depends largely on the recipient vessels for the microvascular anastomoses. Usually the vessels in the axilla (thoracodorsal or circumflex scapular) are preferred for microvascular anastomoses because they have been exposed by the breast surgeon during axillary dissection; the contralateral flap vessels are then preferred. If no axillary dissection is planned, either the internal mammary or axillary vessels may be used, depending on the preference and experience of the surgeon^{81,110–112}.

Comparisons with pedicled TRAM flaps show distinct advantages in favour of the free flap. Schusterman *et al.*¹⁰⁶ reported 7 per cent partial flap loss or fat necrosis for the latter *versus* 13–41 per cent for pedicled flaps^{3,18,66,77,88,90,104,105,113,114}. Fat necrosis is a common occurrence in pedicled flaps, with an incidence 10–50 per cent. This manifests as subcutaneous firmness which often causes anxiety in patients and surgeons in view of its differential diagnosis as recurrent cancer. There is also less rectus muscle and fascia harvested with free flaps and so a reduced incidence of abdominal wall bulges and hernias^{77,106}; there is less functional muscle weakness¹¹⁵. The incidence of abdominal wall hernia after free flap reconstruction is 3–6 per cent^{77,106} compared with 12 per cent for pedicled flaps^{4,66,105,113}. Free TRAM flaps avoid the bulge in the epigastrium that is often caused by tunnelling of pedicled flaps. In immediate breast reconstruction Elliott *et al.*¹⁰⁴ found shorter hospital stays and a decreased incidence of fat necrosis with free flaps. However, in sharp contrast to all of the above, one study has shown no significant difference in outcome and complications between 53 pedicled and 72 free flaps after a 20-month follow-up¹¹⁶.

Free deep inferior epigastric perforator flap

The deep inferior epigastric perforator (DIEP) flap is the latest innovation in TRAM flap breast reconstruction which, in contradistinction to all the above variants, preserves the whole of the rectus muscle and sheath^{79–81,84}. This flap is composed only of the essential parts required for reconstruction, i.e. skin and fat. It is based on one, two or three perforators of the deep inferior epigastric vessels. Vascularity is not compromised and the incidence of fat necrosis is no different from that of the standard free TRAM flaps^{80,83,84}. The advantages of perforator flaps in general, and of DIEP flaps in particular, are the avoidance of muscle sacrifice, hernias and bulges, and decreased postoperative pain and hospital stay. It also avoids a tight fascial closure and the use of synthetic mesh. The former reduces pain and

allows the patient to be mobilized on the first postoperative day with only oral analgesia^{80,117}.

The operation involves a tedious and somewhat nerve-racking dissection that typically adds 1.5 h to the free TRAM flap harvest⁸². Despite current enthusiasm for this procedure to the extent that it is the main or only TRAM flap procedure undertaken in pioneering centres^{80,82,84}, the indications are still being refined. It should, however, be the procedure of choice in: (a) young women (less than 55 years) requiring free TRAM flap breast reconstruction as they will benefit from an intact and previously unviolated abdominal wall for many years of their remaining life; (b) those who may later become pregnant and distend the abdomen (prevents hernia formation) even though pregnancy can be successful after pedicled TRAM flap surgery¹¹⁸; (c) athletic patients for whom abdominal wall integrity is important; and (d) those having simultaneous bilateral breast reconstruction, because the avoidance of sacrifice of the anterior rectus sheath and the rectus abdominis muscle significantly decreases donor site morbidity.

Latissimus dorsi musculocutaneous flap (Fig. 7)

The LD musculocutaneous flap was previously widely used for coverage of mastectomy defects. More recently it has regained popularity with advances in tissue expander and implant design^{51,52,54,55}, the description of the total autologous LD breast reconstruction technique^{86,119–123} and endoscopic techniques of harvest¹²⁴.

The flap is based on the thoracodorsal vessels and it may be transposed anteriorly for breast reconstruction as a musculocutaneous flap with a variable skin paddle, a muscle flap (unusual even for immediate reconstruction) or as an extended completely autogenous flap with overlying fat. Initially developed to provide cover for breast implants, it can provide enough soft tissue on its own to reconstruct small to moderately sized breast defects. Indications in immediate breast reconstruction include: (a) coverage of an expander-implant reconstruction (main use); (b) patients with skin insufficiency after mastectomy but who have insufficient lower abdominal tissue or are medically unfit for a TRAM flap; (c) previously irradiated patients undergoing completion mastectomy; and (d) reconstruction in patients who have already undergone an abdominoplasty or a TRAM flap procedure for the contralateral breast.

In immediate reconstruction following skin-sparing mastectomy the skin requirement is small or none, thereby allowing most or all of the LD skin paddle to be de-epithelialized and buried for increased projection. It is also an excellent option for salvaging partial TRAM flap necrosis in which debridement has left the patient with a distorted reconstructed breast¹²⁵.



Fig. 7 Latissimus dorsi flap skin paddle utilizing a natural skin fold and demonstrating the angle of the scapula, surface marking of the latissimus dorsi muscle and its arterial supply

Standard latissimus dorsi myocutaneous flap

This is the commonest type of LD flap. The skin paddle on the back may be variously sited or oriented depending on the mastectomy defect. The oblique (superolateral to inferomedial) skin paddle column has the best blood supply as it is centred over the anterolateral border of the muscle. It is the easiest to design, raise and insert. The resultant low oblique scar can be easily hidden. This low oblique orientation ideally suits the chest requirements of modified radical mastectomy as the skin island and muscle both need to be located inferiorly. The transverse (horizontal) skin paddle column results in a higher transverse scar that can be easily hidden in the bra-line, unlike the preceding type. Patient input in the choice of scar is important. This design is ideal for radical mastectomy defects in which muscle replacement of the pectoralis major is required. It also places the scar inconspicuously in the bra-line. The oblique (superomedial to inferolateral) skin paddle (skin crease) is more appropriate for patients undergoing skin-sparing mastectomy because the orientation at flap inset is not a problem. The scar sits along the crease line producing the best cosmetic donor site. The excess skin is de-epithelialized and buried under the skin-sparing mastectomy skin flaps. In this situation, where little skin is required, the scar on the back can be reduced dramatically by endoscopically-assisted LD flap harvest.

Extended total autogenous latissimus dorsi myocutaneous flap

In this variety, most or all of the fat overlying the whole of the LD muscle is used to increase the bulk of the flap and so form a larger breast. In its classical form the harvest is at the

level of Scarpa's fascia. Another form, to increase further the bulk, involves a harvest at subdermal level. Significant obesity is one of the key indications for the autogenous LD musculocutaneous flap. Although obese patients have more than enough TRAM tissue, they are at high risk of abdominal wall complications and partial TRAM flap loss. Additionally, the obese have adequate thickness of fat on the back. The pedicled LD flap can be rapidly and safely harvested but it is important to leave enough subdermal or subcutaneous fat under the back skin to avoid skin flap necrosis. There is an increased incidence of seroma formation in obese patients but this is short lived and can be treated simply by aspiration.

The skin paddle in the total autogenous technique for immediate breast reconstruction can be a small straight ellipse that is oriented according to the patient's preferred back donor site. The total autogenous technique is especially suitable for immediate reconstruction because the excess muscle and fat, which are folded underneath the skin paddle, contribute to the breast volume and this increased amount of tissue can be buried under the chest wall flaps to obtain projection ptosis. Although simpler than the TRAM flap and with a shorter recovery time, the volume obtained is often not as large. The final result is not as natural, and the donor site and contour deformity are not as well tolerated. The autogenous LD flap may be combined with an implant in extremely thin patients lacking adequate tissue at any other donor site. An expander technique is preferable because of the greater flexibility in choosing the final implant size and second-stage adjustment of the breast mound.

Muscle flap

In immediate breast reconstruction, the pure muscle flap alone is feasible only for skin-sparing mastectomy or subcutaneous mastectomy where no extra skin is required. It is especially amenable to endoscopic harvest, thereby avoiding large back scars. Its commonest use is to provide muscle coverage for an implant or expander. The advantages of the LD flap are its reliable robust blood supply, associated with the versatility of the skin paddle orientation, and the ease and speed with which it can be performed. The hardy blood supply allows it to be used safely in patients who are high-risk candidates for a pedicled TRAM flap. It involves a much smaller operation than the TRAM flap and gives predictable results with few complications. The scar on the back may be minimized with endoscopic techniques or counterincisions in the axilla.

The drawbacks of the LD flap of specific relevance to immediate reconstruction relate to the donor site, the flap and the (often associated) prosthesis. The commonest postoperative complication is seroma formation at the back

donor site and this often requires repeated aspiration before it settles. Its reported incidence ranges from 9 to 33 per cent^{123,126–129}. Significant flap necrosis is rare and is nearly always associated with recognized or unrecognized injury to the vascular pedicle^{126,130,131}. Partial flap necrosis occurs in up to 7 per cent of cases, but is more common in the extended total autogenous variant, or when the skin paddle is placed too distally over the aponeurotic part^{22,121,123,126,127,131}. Capsular contracture in association with combined LD flap and silicone gel breast implant reconstruction was historically common (up to 40 per cent)^{126,127,132,133}. When the LD flap is used with saline-for-gel substitution and prosthetic surface texturing, significant capsular contracture is unusual^{26,134}. Slippage of the expander or implant through the axilla and into the back is rare but is more likely to occur in immediate reconstruction because of the wide communication between the mastectomy, axillary dissection and back donor sites¹²⁶. It can be prevented by suturing the LD muscle to the lateral chest wall.

Other autogenous tissue techniques

Although these all require microvascular surgical transfer, they are important secondary choices. Because of the uniform requirement for microsurgical expertise and the excellent results obtained from TRAM and LD flap reconstruction, their use is restricted to patients seeking autogenous tissue reconstruction who: (a) have insufficient abdominal or back tissue; (b) do not want scars on the back or abdomen; (c) have had numerous previous abdominal or chest wall operations precluding the use of TRAM or LD flaps; (d) have previously used the TRAM flap for an earlier unilateral breast reconstruction or an abdominoplasty; and (e) have had a failed pedicled or free TRAM flap.

Superior gluteal free flap

The gluteus maximus myocutaneous free flap for breast reconstruction was first introduced in 1983 by Shaw^{110,135}. The superior gluteal free flap is based on the superior gluteal artery and vein. Although a large amount of vascularized fat and overlying skin can be reliably moved to the chest wall to create a new breast, its size depends on the size of the patient's buttocks. The donor site is well hidden and matches the opposite side quite well in individual cases.

Inferior gluteal free flap

The inferior gluteal free flap^{23,24,136} is preferred to the superior version because of its longer vascular pedicle,

which is easier to dissect, and because even in the thin patient it has more available tissue. The natural breast contour and shape obtained stem from its thickness, consistency and the large amounts of fat and skin available. It has excellent vascularity and only a small amount of muscle is needed to provide musculocutaneous perforators for the much larger overlying skin and fat island. Its drawbacks include the need for microsurgery, repositioning during the operation and (frequently) the need for vein grafts to establish microanastomoses on the chest wall. It also requires a more difficult dissection than free TRAM flap harvest. The inferior gluteal donor site scar can sometimes be painful. Sciatica may result from taking too much muscle with the flap, thereby leaving the sciatic nerve devoid of a suitable pad. Seroma is also frequent at the donor site.

Gluteal perforator free flaps

Both the superior and inferior gluteal flaps can be raised as perforator flaps, totally preserving the muscles and utilizing only the skin and fat¹¹⁷. The superior gluteal perforator flap has been used successfully for immediate reconstruction.

Lateral transverse thigh flap

The lateral transverse thigh flap uses skin and fat from the upper lateral thigh based on the lateral circumflex femoral vessel blood flow into the tensor fascia lata muscle^{17,25}. It may be utilized either unilaterally or bilaterally. In the latter, the two transfers may be performed simultaneously or staged from a few days to a month apart. Its disadvantages are the more visible scar on the lateral thigh compared with TRAM or gluteal flap scars, the need for microsurgery, and donor site seromas which can be persistent¹⁷. It also creates a contour deformity in the upper thigh. As for the Taylor–Rubens flap, the unilateral donor site usually requires a balancing procedure on the opposite side; this may be achieved with liposuction.

Taylor–Rubens peri-iliac free flap

This consists of the skin and soft tissue portion of the deep circumflex iliac artery flap described by Taylor *et al.* in 1979^{137,138}. Its indications are the same as for the other non-TRAM, non-LD, autogenous tissue reconstructions. It is an ideal alternative when the TRAM flap is not available because the patient has previously undergone a TRAM flap procedure or abdominoplasty. Another specific indication is in patients in whom there is insufficient lower abdominal fat, but adequate fat in the flank and peri-iliac crest area. Its

main drawback is the violation of the integrity of the lateral abdominal wall and the possibility of flank herniation if the donor site is not closed properly.

Inframammary fold

The inframammary fold is a key landmark in defining the breast contour and it is very important that it is not destroyed during mastectomy. Marking its position, such that it is clearly visible during operation, helps to avoid its unnecessary violation. However, if it is destroyed it may be recreated during surgery before insertion of the prosthesis using the internal suturing technique, carefully avoiding inadvertent exteriorization of the sutures (an infection risk). Other techniques of recreating the inframammary fold are more appropriate for delayed reconstruction or expander-to-implant exchange; such detail is beyond the scope of this review.

Aesthetic, oncological and psychological considerations

Skin-sparing mastectomy

Skin-sparing mastectomy was introduced in 1991 by Toth and Lappert¹⁴⁰. It entails the careful preoperative planning of mastectomy skin incisions with the express aim of maximizing skin preservation in order to facilitate reconstruction of the breast mound and enhance its aesthetics^{141–145}. It removes the breast, nipple-areolar complex, previous biopsy incisions (if feasible) and skin overlying superficial tumours^{140,145–148}. The use of skin-sparing incisions does not increase the complication rate or compromise local disease control. Kroll *et al.*¹⁴¹, for instance, reported only one local recurrence after a 2-year follow-up of 100 patients with breast cancer treated by skin-sparing mastectomy and immediate reconstruction.

Preoperative and peroperative communication and co-operation between the oncological surgeon and the reconstructive surgeon is vital to ensure success of skin-sparing techniques^{85,140}. The reconstructive advantages are that preservation of the native skin reduces the amount of tissue transfer required, while preservation of the inframammary fold and native skin envelope facilitates breast shaping during reconstruction and reduces the extent of balancing surgery on the contralateral breast needed to achieve symmetry. In addition, the periareolar incisions are inconspicuous. It is technically more demanding and time consuming than a modified radical mastectomy. The skin flaps must be handled gently to avoid ischaemic complications and the procedure should be used with caution in smokers or those who have had chest wall irradiation. A

recent review of the Emory University experience of 331 cases of skin-sparing mastectomy described a 10 per cent incidence of native skin flap necrosis¹⁴³. In practice, most skin-sparing mastectomies are followed by autogenous tissue reconstruction, especially with the TRAM flap^{85,147}. When tissue expander reconstruction is used, it is often possible to close the circular periareolar incision completely with a purse-string suture.

Oncological considerations

Breast reconstruction after mastectomy was traditionally performed as a delayed procedure because it was feared that immediate reconstruction would delay or increase the complications following adjuvant treatment, such as radiotherapy or chemotherapy. An additional concern was that the presence of a reconstructed breast might delay or interfere with the diagnosis of local recurrence. The incidence of local recurrence following mastectomy and immediate reconstruction of all types ranges from 0 to 11 per cent^{45,104,113,149–158}. Several of the relevant studies compared patients who had reconstruction with those who did not have immediate reconstruction, and no significant difference in local recurrence was detected once the groups had been corrected for tumour size, grade and node positivity^{149,151,155}. It is well documented that the majority of local recurrences are located in the skin flaps following mastectomy^{156,159}. Slavin *et al.*¹⁵⁶ reported that all local recurrences following reconstruction were detected on follow-up clinical examination, and that no delay in diagnosis was due to the reconstructed breast. Furthermore, the presence of a reconstruction did not compromise the treatment of recurrence. Women undergoing immediate breast reconstruction have similar survival rates to women who do not have reconstruction^{150,153}. Furthermore, there is no significant difference in survival between patients who undergo immediate or delayed reconstruction¹⁵¹.

Immediate reconstruction does not delay the administration of adjuvant radiotherapy or chemotherapy^{156,160–162}. It has been suggested by some that early complications of reconstruction might delay chemotherapy¹⁶³, but others have found that this is not so^{4,64,155,160}. Rosen *et al.*⁴, for instance, found no delay in administering adjuvant chemotherapy in 23 patients following reconstruction with either tissue expansion or myocutaneous flaps. In a non-randomized comparison of pedicled and free TRAM flaps, Schusterman *et al.*⁹³ found a non-significant trend towards less delay in chemotherapy in patients who had had free TRAM flaps. Significant additional morbidity with delay of chemotherapy has not been noted with either breast implants¹⁶¹ or autogenous tissue¹⁵⁸.

The morbidity associated with reconstruction may be increased by the various adjuvant therapies for breast cancer, and the cosmetic results may be worse than in those not subjected to adjuvant treatment^{47,164}. This is especially so with radiotherapy and prosthetic reconstruction. Dickson and Sharpe⁴⁷ found a significantly increased risk of capsular contracture in prosthetic recipients who had postoperative radiotherapy. This has been confirmed independently by others^{41,49,60,163,165–168}. Barreau-Pouhaer *et al.*¹⁶³ reported an increased risk of implant failure in patients undergoing postoperative radiotherapy where 'failure' was defined as implant removal. Expanding irradiated tissues is more difficult and painful, and the final reconstructed breast is often too small and hard, without natural ptosis^{164,169}. Patients who undergo adjuvant chemotherapy and radiotherapy also have worse cosmetic results than those not subjected to adjuvant treatment¹⁶⁴. The effect of radiation on reconstruction performed using myocutaneous flaps has been the subject of recent attention^{162,169–171}. Hunt *et al.*¹⁷¹ found no significant increase in complications following TRAM flap reconstruction and radiotherapy in a group of 19 patients. Zimmerman *et al.*¹⁷⁰ studied 21 patients who had free TRAM flap reconstruction followed by radiotherapy. They found no flap-related complications, and the cosmetic results were rated good to excellent by 90 per cent of the patients. In contrast, the Emory University group found radiation changes in ten of 19 TRAM flaps subjected to postreconstruction radiotherapy and six of these patients consequently required surgery to the flap¹⁶⁹. In general, however, TRAM flaps tend to tolerate irradiation well and so, if radiotherapy is required, it is sensible to avoid prosthetic reconstruction and preferentially resort to autogenous reconstruction.

Contralateral breast

When the reconstructed breast cannot match its partner, reduction mammoplasty and mastopexy are routinely undertaken to improve symmetry; this is done at the time of mastectomy and immediate breast reconstruction. This allows greater flexibility for second-stage revision and should reduce the overall cost of breast reconstruction. The breast reduction technique should avoid fat necrosis or excessive internal scarring. Liposuction of the breast during the reduction should be avoided because of the possibility of inducing macrocalcification. Occasionally breast augmentation to achieve symmetry is indicated. While mastopexy and reduction cause some alteration of the mammographic image of the normal breast, such change does not generally interfere with surveillance¹⁷². In contrast, augmentation mammoplasty (especially subglandular placement) changes

the ability to interpret postoperative mammograms and implant displacement mammography techniques are required¹⁷³.

Immediate nipple reconstruction

Creating a nipple-areolar complex is an integral part of breast reconstruction. It enhances the final cosmetic result, creates a more realistic and more natural-looking reconstructed breast, and significantly increases patient satisfaction¹⁷⁴. There are numerous techniques for nipple reconstruction². Free grafts of tissue may be taken from the contralateral nipple (nipple sharing), ear lobule, labia minora or toe pulp^{175–177}.

Nipple sharing allows a perfect match of colour and texture, but may overly reduce and distort the otherwise normal donor nipple, and reduce its sensation, while producing only slight projection of the new nipple. It is reserved for patients willing to sacrifice 50 per cent of the height of a prominent nipple on the normal breast. Worldwide, the commonest method of nipple reconstruction is the use of local flap techniques based on the new breast mound such as the skate/quadrupod, modified skate, mushroom, star, C-V, S, maltese cross and other flaps^{175,178,179}. The choice of technique is largely dependent on the experience of the surgeon. It is important to remember that, with time, almost all flap techniques lose more than 50 per cent of their size in terms of projection.

Immediate nipple reconstruction is feasible but requires well vascularized autogenous tissue such as the free TRAM flap or the total autogenous LD flap^{73,180,181}. It involves creating a central 'dog ear', i.e. leaving excess tissue on the flap at the proposed location of the nipple. At present it cannot be recommended because exact nipple location is difficult. In addition, it may compromise the blood supply to the breast flap or to the nipple flap.

Immediate areolar reconstruction with a skin graft from the inner thigh, labia minora, opposite areolar or trunk dog ears has now been superseded by later intradermal tattooing of the skin that surrounds the newly reconstructed nipple. This is carried out 2–3 months after nipple reconstruction^{2,61,182,183}. Areolar sharing, unless it is carried out at the time of a planned contralateral breast reduction, can significantly distort the otherwise normal-looking nipple-areolar complex¹⁶. Although tattooing of the nipple-areolar complex can be undertaken before nipple reconstruction, it is mostly undertaken afterwards, as popularized by Spear *et al.*¹⁸³. Artificial nipples may be used; although they look realistic they have not gained popularity with patients.

Psychological considerations

Although this is a complex subject, it is well recognized that early breast reconstruction significantly reduces the psychological morbidity of mastectomy^{174,184–187}. There are many psychological effects of mastectomy^{188–193}. Notable among these are feelings of mutilation and altered body image, diminished self-worth, loss of a sense of femininity, decrease in sexual attractiveness and function, anxiety, depression, hopelessness, guilt, shame, fear of recurrence and abandonment^{188–193}. Most difficulties in the long term, however, relate to body image and sexual functioning¹⁹³.

It is anticipated that immediate reconstruction will spare women the pain of disfigurement and loss that accompanies mastectomy¹⁹⁴. Women undergoing immediate reconstruction not only have high levels of satisfaction with the surgical results, but also significantly less psychosocial morbidity than those undergoing mastectomy alone^{174,184,185,187,194,195}. They are less depressed, and experience less impairment of their sense of femininity, self-esteem and sexual attractiveness than their peers who delayed or did not seek reconstruction. They also tend to accept the new breast as an integral part of their body¹⁸⁵. They have significantly less 'distress' in recalling the surgery¹⁷⁴, are less likely to be 'repulsed' by their own naked appearance, and have more freedom to dress than women who do not have reconstruction^{184,185}. However, there may be a selection bias in these results in that patients who want and demand immediate breast reconstruction may be a self-selected and well-motivated group who therefore show the most benefit.

The psychological benefits of immediate breast reconstruction are greater than those of delayed reconstruction and compare favourably with breast conservation therapy in psychosocial outcome. In one comparison of immediate *versus* delayed breast reconstruction, there was lower postoperative psychological morbidity in the former¹⁸⁵. In an uncontrolled study, Noone *et al.*¹⁹⁴ found improved self-image and less psychological turmoil following immediate reconstruction. In another non-randomized study, Dean *et al.*¹⁸⁴ demonstrated significant psychological advantages to immediate reconstruction compared with delayed reconstruction. Schain¹⁸⁷ found that women who underwent immediate or early reconstruction (less than 1 year after mastectomy) had significantly less recalled distress regarding the mastectomy than women who had a delayed reconstruction. Patients seeking reconstruction after mastectomy are primarily motivated by a desire for wholeness¹⁸⁷. Handel *et al.*¹⁹⁶ examined the reasons why women did not have reconstruction following mastectomy, and found that advanced age, concern about complications from more extensive surgery, uncertainty about the outcome and

anxiety about the effect of reconstruction on breast cancer all deterred women from reconstruction. Marital status, need for adjuvant therapy, or personal experience of poor results from reconstruction did not influence decision-making. More recently, Rosenqvist *et al.*¹⁵⁰ found high levels of patient satisfaction following immediate reconstruction, although they point out that high levels of preoperative information and psychological support were necessary.

However, the advantages of breast reconstruction may not be universal. It was suggested in one early study that the initial differences in adjustment between reconstructed and non-reconstructed patients might be minimal and disappear with time¹⁸⁷. Similarly, Rolland¹⁹⁷ suggested that satisfaction with the technical aspects of the reconstructive outcome might be slightly lower among earlier than later reconstructed patients¹⁹⁷. This large prospective study of women's response to reconstruction found that the greater the time since mastectomy, the greater the patient's satisfaction with the overall results of the reconstruction.

Health economics

This area is poorly addressed in the literature. In a direct comparison of costs to hospitals, delayed breast reconstruction was 62 per cent more expensive to perform than immediate breast reconstruction after completion of the entire reconstruction process, including nipple-areolar reconstruction¹⁹⁸. Although the initial costs of prosthetic reconstruction are lower than those of autogenous tissue reconstruction, with time the costs of the former increase significantly for a number of reasons. The prime reason is the need for revisional surgery with prosthetic surgery. Tissue expanders need to be exchanged for permanent implants, capsular contracture needs reoperation plus implant exchange, and deflated or ruptured implants need replacement. A study comparing the cost of TRAM flaps and prosthetic reconstructions found that the long-term cost of TRAM flap reconstruction did not increase as much as that of implant-based reconstruction and was cumulatively lower than that of tissue-expander implants. This differential cost is likely to increase with time¹⁹⁹.

Conclusion

Immediate breast reconstruction is a safe and acceptable procedure after mastectomy for cancer. There is no evidence that it has oncologically untoward consequences. In the appropriate patient it can be achieved effectively with either prosthetic or autogenous tissue, but careful patient selection is important to optimize results and minimize

complications. Careful counselling of the patient about available options and the need for future revisional surgery, particularly with prosthetic reconstruction, is important. Ideally, the oncological and reconstructive surgeons should discuss and plan surgery together, and communicate closely during the operation (especially in skin-sparing mastectomy and autogenous reconstruction). Although autogenous tissue techniques give the best aesthetic and most natural results, they are a more significant surgical undertaking. Finally, it should be appreciated that recent innovations in expander and implant design have made the results of prosthetic reconstruction more predictable.

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Duodenal injuries

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Background: The worldwide increase in road traffic accidents and use of firearms has increased the incidence of duodenal trauma.

Methods: The English language literature on duodenal trauma over the period 1970–1999 was reviewed.

Results and conclusion: Upper gastrointestinal radiological studies and computed tomography may lead to the diagnosis of blunt duodenal trauma. Exploratory laparotomy remains the ultimate diagnostic test if a high suspicion of duodenal injury continues in the face of absent or equivocal radiographic signs. The majority of duodenal injuries may be managed by simple repair. More complicated injuries require more sophisticated techniques. High-risk duodenal injuries are followed by a high incidence of suture line dehiscence and they should be treated by duodenal diversion. Pancreaticoduodenectomy should be considered only if no alternative is available. 'Damage control' should precede definitive reconstruction.

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Introduction

Duodenal injury can pose a formidable challenge to the surgeon and failure to manage it properly may have devastating results. The total amount of fluid passing through the duodenum exceeds 6 l/day and a fistula in this area may cause serious fluid and electrolyte imbalance. A large amount of activated enzymes liberated into the retroperitoneal space and the peritoneal cavity may be life threatening. A preoperative diagnosis of isolated duodenal injury can be very difficult to make and there is no single method of duodenal repair that completely eliminates the possibility of dehiscence of the duodenal suture line. As a result, the surgeon is confronted with the dilemma of choosing between several preoperative investigations and many surgical procedures. Detailed knowledge of the available operative choices and their correct application is important.

Diagnosis

Penetrating trauma is the leading cause of duodenal injury in countries with a high incidence of civilian violence, such as the USA and South Africa; 75–80 per cent of this trauma is due to gunshot wounds¹. In the more peaceable environment of western Europe, blunt injury is the most likely cause. The retroperitoneal location of the duodenum

and its close proximity to a number of other viscera and major vascular structures means that isolated penetrating injury of the duodenum itself is rare. The need for abdominal exploration is usually dictated by associated injuries and the diagnosis of duodenal injury is usually made in the operating room. Particularly for gunshot wounds, a trajectory into the abdomen always warrants exploration in the authors' opinion².

Blunt injury of the duodenum is both less common and more difficult to diagnose than penetrating injury, and it may typically occur in isolation or with pancreatic injury. It usually occurs from crushing of the duodenum between spine and steering wheel, handlebar or some other force applied to the anterior aspect of the abdomen. Such injury may be associated with flexion/distraction fracture of L1–L2 vertebrae (the Chance fracture). 'Stomping' and striking the mid-epigastrium are common. Less commonly, deceleration may produce a tear at the junction of the third and fourth parts of the duodenum, and tears of the first and second parts have occasionally been reported. These injuries occur at the junction of free (intraperitoneal) parts of the duodenum with fixed (retroperitoneal) parts. A high index of suspicion, based on mechanism of injury and physical examination, may lead to further diagnostic studies.

The initial clinical changes in isolated duodenal injury may be extremely subtle before severe, life-threatening,

peritonitis develops. In the vast majority of retroperitoneal perforations there is at first only mild upper abdominal tenderness with a progressive rise in temperature, tachycardia and occasionally vomiting. After several hours the duodenal contents extravasate into the peritoneal cavity with the development of peritonitis. If these contents spill into the lesser sac they are usually 'walled off' and localized, although occasionally they may leak into the general peritoneal cavity via the foramen of Winslow, with resultant generalized peritonitis³. Diagnostic difficulties do not arise in those patients in whom blunt injury causes intraperitoneal perforation.

Theoretically, duodenal perforation should be associated with a leak of amylase and other digestive enzymes, and it has been suggested that determination of the serum amylase concentration may be helpful in diagnosis^{4,5}. The test lacks sensitivity^{6,7}. The duodenum is retroperitoneal, the concentration of amylase in the fluid that leaks is variable, and amylase concentrations often take hours to days to increase after injury. Although serial determination of serum amylase is better than a single, isolated assay on admission, sensitivity is still poor and serial determination involves necessary delay in treatment. If the serum amylase level is raised on admission, a diligent search for duodenal rupture is warranted. The presence of a normal amylase level, however, does not exclude duodenal injury⁸. Although virtually all patients with blunt duodenal injury will eventually have an increased white blood cell count and amylase level in diagnostic peritoneal lavage fluid, such lavage has a low sensitivity for diagnosis of duodenal perforation^{9,10}.

Radiological studies may be helpful in the diagnosis. Plain radiographs of the abdomen are useful when gas bubbles are present in the retroperitoneum adjacent to the right psoas muscle, around the right kidney, or anterior to the upper lumbar spine. They may also show free intraperitoneal gas and, although rarely seen, gas in the biliary tree has also been described¹¹. Obliteration of the right psoas muscle shadow or fractures of the transverse processes of the lumbar vertebrae are indicative of forceful retroperitoneal trauma and serve as a predictor of duodenal injury^{5,12}.

An upper gastrointestinal series using water-soluble contrast material provides positive results in 50 per cent of patients with duodenal perforations¹³. Meglumine (Gastrografin; Schering, Berlin, Germany) should be infused via a nasogastric tube rather than swallowed, and the study should be done under fluoroscopic control with the patient in the right lateral position. If no leak is observed, the investigation continues with the patient in the supine and then in the left lateral position. If the Gastrografin study is negative, it should be followed by

administration of barium contrast agent since it allows detection of small perforations more readily³. Upper gastrointestinal studies with contrast media are also indicated in patients with a suspected haematoma of the duodenum, because they may demonstrate the classic 'coiled spring' appearance of complete obstruction by the haematoma^{8,14}.

Computed tomography (CT) has been added to the diagnostic armamentarium for subtle duodenal injury. It is very sensitive to the presence of small amounts of retroperitoneal air, blood or contrast agent extravasated from the injured duodenum, especially in children^{15,16}. Its reliability in adults is more controversial^{15,17}. The presence of periduodenal wall thickening or haematoma without extravasation of contrast material should be investigated with a gastrointestinal study with Gastrografin. If normal, it should be followed by a barium contrast study if the patient's condition allows this³.

Diagnostic laparoscopy does not confer any improvement over more traditional methods in the investigation of the duodenum. Because of its anatomical position, diagnostic laparoscopy is a poor modality for determining organ injury¹⁸.

Exploratory laparotomy remains the ultimate diagnostic test if a high degree of suspicion of duodenal injury continues in the face of absent or equivocal radiographic signs. All patients undergoing a laparotomy for abdominal trauma should be explored through a long midline incision. Upper midline retroperitoneal haematomas should be explored to rule out underlying duodenal, pancreatic or vascular injury. It is wise to ensure that proximal and distal control of the aorta, and distal control of the inferior vena cava, are readily available before the haematoma is explored. Mobilization of the whole duodenum is mandatory for exclusion of duodenal injury. Initially the Kocher manoeuvre is performed by dividing the lateral peritoneal attachment of the duodenum and mobilizing both the second and third parts medially with a combination of sharp and blunt dissection. Entry into the lesser sac by way of the gastrocolic ligament provides exposure of the posterior aspect of the proximal portion of the first part of the duodenum and the medial aspect of the second part. Better inspection of the third part and inspection of the fourth part of the duodenum may be achieved by mobilizing the ligament of Treitz, and performing the Cattell and Braasch manoeuvre. This manoeuvre requires mobilization of the right colon (including the hepatic flexure) from right to left so that the right colon and small intestine may be elevated. The small bowel mobilization is undertaken by sharply incising its retroperitoneal attachments from the lower right quadrant to the ligament of Treitz. It is important to replace the small intestine in the abdominal cavity with

great care at the conclusion of the operation. Iatrogenic volvulus of the mobilized bowel is possible if this is not done. Severe oedema, crepitation or bile staining of the periduodenal tissues implies a duodenal injury until proven otherwise. If the exploration of the duodenum is negative but there is still a strong suspicion of duodenal injury, Brotman *et al.*¹⁹ recommend instillation of methylene blue through a nasogastric tube. Rapid staining of periduodenal tissues is unmistakable evidence of an intestinal leak in this area, and the lack of staining, in their hands, has proven reliable in ruling out full-thickness duodenal injury.

Surgical management of duodenal injury

Grading systems have been devised to characterize duodenal injuries (Table 1). Although useful for research purposes, the specifics of the grading systems are less important than several simple aspects of the duodenal injuries: (a) the anatomical relation to the ampulla of Vater; (b) the characteristics of the injury (simple laceration *versus* destruction of duodenal wall); (c) the involved circumference of the duodenum; and (d) associated injury to the biliary tract, pancreas, or major vascular injury^{21,22}. Timing of the operation is also important as the mortality rate rises from 11 to 40 per cent if the time interval between injury and operation is more than 24 h¹⁸.

From a practical point of view the duodenum may be divided into an upper portion that includes the first and second part, and a lower portion that includes the third and fourth part¹. The upper portion has complex anatomical structures within it (common bile duct and sphincter) and the pylorus. It requires distinct manoeuvres to diagnose injury (cholangiogram, direct visual inspection) and complex techniques to repair them. The first and second parts of

the duodenum are densely adherent and dependent for their blood supply on the head of the pancreas, so diagnosis and management of any injury is complex, and resection, unless involving the entire C loop and pancreatic head, is impossible. The lower portion may generally be treated like small bowel; diagnosis and management is relatively simple, including debridement, closure, resection and reanastomosis¹.

Intramural haematoma

This is a rare injury of the duodenum that is specific to patients with blunt trauma. It is most common in children after isolated force to the upper abdomen, possibly because of the relatively flexible and pliable musculature of the child's abdominal wall; half of the cases can be attributed to child abuse²¹. The haematoma develops in the submucosal or subserosal layers of the duodenum, which is not perforated. Such a haematoma may lead to obstruction. The symptoms of gastric outlet obstruction may take up to 48 h to present as gradual increase in size of the haematoma occurs owing to breakdown of the haemoglobin rendering it hyperosmotic with resultant fluid shifts into it. The diagnosis may be made by double-contrast CT or upper gastrointestinal contrast studies that show the 'coiled spring' or 'stacked coin' sign¹⁵. The injury is usually considered non-surgical and best results are obtained by conservative treatment, if associated injuries can be ruled out^{16,23}. After 3 weeks of conservative management with nasogastric aspiration and total parenteral nutrition, the patient is re-evaluated. If there is no improvement he or she undergoes laparotomy to rule out the presence of duodenal perforation or injury of the head of the pancreas that may be an alternative cause of duodenal obstruction.

The treatment of an intramural haematoma found at early laparotomy is controversial¹. One option is to open the serosa, evacuate the haematoma without violation of the mucosa, and carefully repair the wall of the bowel. The concern is that this may convert a partial tear to a full-thickness tear of the duodenal wall. Another option is carefully to explore the duodenum to exclude a perforation, leaving the intramural haematoma intact, with postoperative nasogastric decompression planned¹.

Duodenal perforation

The great majority of duodenal perforations may be managed with simple surgical procedures. This is particularly true of penetrating injuries where the time interval between injury and operation is usually short. On the other hand, a minority of cases comprises high-risk lesions with an increased likelihood of dehiscence of the

Table 1 Duodenal injury severity according to the American Association for the Surgery of Trauma

Grade	Injury	Description
I	Haematoma	Single portion of duodenum
	Laceration	Partial thickness only
II	Haematoma	Involving more than one portion
	Laceration	Disruption < 50 per cent circumference
III	Laceration	Disruption 50–75 per cent circumference of D2
		Disruption 50–100 per cent circumference of D1, D3, D4
IV	Laceration	Disruption > 75 per cent circumference of D2 Involving ampulla or distal common duct
V	Laceration	Massive disruption of duodenopancreatic complex Devascularization of duodenum

D1, D2, D3, D4: first, second, third, and fourth portions of the duodenum. For multiple injuries, the grade is advanced by one²⁰.

duodenal repair, with increased morbidity and, sometimes, mortality rates. These high-risk injuries are related to associated pancreatic injury, blunt or missile injury, involvement of more than 75 per cent of the duodenal wall, injury of the first or second part of the duodenum, time interval between injury and repair of more than 24 h, and associated common bile duct injury¹. For such injuries several adjunctive operative procedures have been proposed in an attempt to reduce the incidence of dehiscence of the duodenal suture line. Methods of repair of the duodenal injury and supportive procedures against dehiscence are described below.

Repair of the perforation

Most injuries of the duodenum may be repaired by primary closure in one or two layers. The closure should be orientated transversely, if possible, to avoid luminal compromise. Excessive inversion should be avoided. Longitudinal duodenotomies may usually be closed transversely if the length of the duodenal injury is less than 50 per cent of the circumference of the duodenum¹. If primary closure would compromise the lumen of the duodenum, several options have been recommended. Pedicled mucosal graft, using a segment of jejunum or a gastric island flap from the body of the stomach, has been suggested as a method of closing large duodenal defects^{24,25}. Another possibility is the use of a jejunal serosal patch to close the duodenal defect^{26,27}. The serosa of the loop of jejunum is sutured to the edges of the duodenal defect. Although encouraging in experimental studies, the clinical application of both of these methods is limited and suture line leaks have been reported²⁸. Laying a loop of jejunum on to the area of the injury such that the serosa of the jejunum buttresses the duodenal repair has also been suggested²⁹. No beneficial results have been reported from this technique^{30,31}.

In complete transection of the duodenum, the preferred method of repair is primary anastomosis of the two ends after appropriate debridement and mobilization¹¹. It is frequently the case with injuries of the first, third and fourth part of the duodenum that mobilization is technically not difficult. However, if a large amount of tissue is lost, approximation of the duodenal ends may not be possible without producing undue tension on the suture line. If this is the case and complete transection occurs in the first part of the duodenum, antrectomy should be performed with closure of the duodenal stump and a Bilroth II gastrojejunostomy. When such injury occurs distal to the ampulla of Vater, closure of the distal duodenum and Roux-en-Y duodenojejunal anastomosis is appropriate³². Mobilization of the second part of the duodenum is limited by its shared

blood supply with the head of the pancreas. A direct anastomosis to a Roux-en-Y loop sutured over the duodenal defect in an end-to-side fashion is the procedure of choice. This may also be applied as an alternative method of operative management of extensive defects of the other parts of the duodenum when primary anastomosis is not feasible. External drainage should always be provided because it affords early detection and control of duodenal fistula. The drain is preferably a simple, soft silicone rubber, closed system placed adjacent to the repair³².

Duodenal diversion

In high-risk duodenal injury, repair is followed by a high incidence of suture line dehiscence. To protect the repair, the gastrointestinal contents with their proteolytic enzymes may be diverted, a practice that also makes the management of a duodenal fistula easier.

Tube decompression was the earliest technique used for decompression of the duodenum and diversion of its contents in an attempt to preserve the integrity of the duodenorrhaphy. It was first described in 1954 as a method of management of a precarious closure of the duodenal stump after a gastrectomy³³. The technique was introduced for trauma by Stone and Garoni as a triple ostomy³⁴. This consists of a gastrostomy tube to decompress the stomach, a retrograde jejunostomy to decompress the duodenum, and an antegrade jejunostomy to feed the patient. The initially favourable reports on the ability of this technique to decrease the incidence of dehiscence of the duodenorrhaphy have not been supported by more recent work^{11,31,35}. The drawbacks of the technique include several new perforations being made in the gastrointestinal tract, the inefficiency of the jejunostomy tube in decompressing properly the duodenum, and the common scenario of the drains falling out or being removed by the patient³. The fashioning of a feeding jejunostomy at the initial laparotomy in patients with duodenal injury and extensive abdominal trauma (Abdominal Trauma Index greater than 25) is highly recommended¹¹.

Duodenal diverticulation, as originally described, includes a distal Billroth II gastrectomy, closure of the duodenal wound, placement of a decompressive catheter into the duodenum and generous drainage of the duodenal repair³⁶. Truncal vagotomy and biliary drainage might be added. The disadvantage of duodenal diverticulation is that it is an extensive procedure that is totally inappropriate for the haemodynamically unstable trauma patient or the patient with multiple injuries. Resection of a normal distal stomach cannot be beneficial and should not be considered unless there is a large amount of destruction and tissue loss, and no other course is possible.

Pyloric exclusion was devised as an alternative to the above extensive procedure to shorten the operative time and make the procedure reversible. After primary repair of the duodenum, a gastrotomy is made at the antrum along the greater curvature. The pyloric ring is grasped and invaginated outside the stomach through the gastrotomy, and is closed with a large running suture or by stapling. The closed pyloric ring is returned into the stomach and a gastrojejunostomy is fashioned at the gastrotomy site (Fig. 1). The closure of the pylorus breaks down after several weeks and gastrointestinal continuity is re-established. This occurs regardless of whether the pylorus is closed with absorbable suture, non-absorbable suture or stapler³⁷. Concern has been expressed about the ulcerogenic potential of the pyloric exclusion, as marginal ulceration has been reported in up to 10 per cent of cases^{37,38}. The long-term incidence of marginal ulceration in patients who underwent pyloric exclusion is probably underestimated; it is notoriously difficult to achieve adequate long-term follow-up in the trauma population. In line with others, the authors do not practice vagotomy with pyloric exclusion³⁹. Ginzburg *et al.*⁴⁰ question the need to perform routine gastrojejunostomy after pyloric exclusion, taking into consideration that continuity of the gastrointestinal tract will be re-established in 90 per cent of patients within 3 weeks. A duodenal fistula may still occur with pyloric exclusion, and there is concern that spontaneous opening of the pyloric sphincter will negatively influence closure of the fistula. This has been shown not to be a clinically relevant problem⁴¹. Pyloric exclusion is a technically easier, less radical and quicker operation than diverticulation of the duodenum, and appears to be equally effective in the protection of a duodenal repair⁴²⁻⁴⁵. An interesting technique of controlled reopening of the pyloric exclusion is reported by Fang *et al.*⁴⁶. The use of octreotide in protection of the suture line in pancreaticojejunostomy after pancreaticoduodenectomy has been shown to be beneficial^{47,48}. Its application following duodenal trauma

for protection of the duodenal repair has been suggested by Mullins *et al.*⁴⁹. The principle is attractive, but further experience is required before sound conclusions can be drawn.

Pancreaticoduodenectomy

This is a major procedure that should only be practised in the trauma situation if no alternative is available. Damage control, with control of bleeding and bowel contamination, and ligation of the common bile and pancreatic ducts, should be the rule⁵⁰. Reconstruction should take place within the next 48 h when the patient is stable. Indications for considering pancreaticoduodenectomy are massive disruption of the pancreaticoduodenal complex, devascularization of the duodenum and, sometimes, extensive injury to the second part of the duodenum involving the ampulla or distal common bile duct^{3,50-52}.

The role of pancreaticoduodenectomy in trauma is best summarized by Walt⁵³: 'Finally, to Whipple or not to Whipple, that is the question. In the massively destructive lesions involving the pancreas, duodenum and common bile duct, the decision to do a pancreaticoduodenectomy is unavoidable; and, in fact, much of the dissection may have been done by the wounding force. In a few patients, when the call is of necessity close, the overall physiologic status of the patient and the extent of damage become the determining factors in the decision. Though few in gross numbers, more patients are eventually salvaged by drainage, total parenteral nutrition and meticulous overall care than by a desperate pancreaticoduodenectomy in a marginal patient'.

Specific injuries

Simple combined injuries of the pancreas and duodenum should be managed separately. More severe injuries require more complex procedures. Feliciano *et al.*⁵⁴ have reported by far the largest experience of combined pancreaticoduodenal injuries and suggest that (a) simple duodenal injury with no ductal pancreatic injury (grades I and II) should be managed with primary repair and drainage (Table 2); (b) grade III duodenal and pancreatic injuries are best treated with repair or resection of both organs as indicated, pyloric exclusion, gastrojejunostomy and closure; and (c) grade IV and V duodenal and pancreatic injuries are best treated by pancreaticoduodenectomy.

Extensive local damage of the intraduodenal or intrapancreatic bile duct frequently necessitates a staged pancreaticoduodenectomy. Less extensive local injuries may be managed by intraluminal stenting, sphincteroplasty or reimplantation of the ampulla of Vater^{11,55-57}.

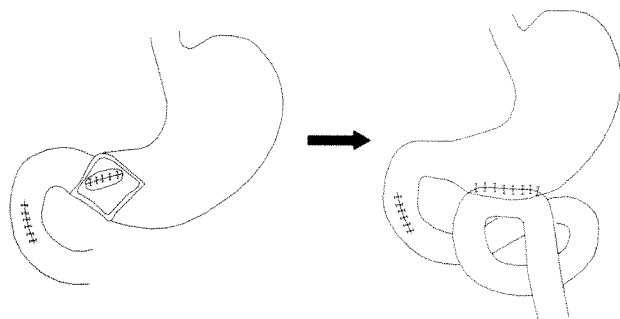


Fig. 1 Pyloric exclusion

Table 2 Pancreatic injury severity according to the American Association for the Surgery of Trauma

Grade	Injury description
I	Minor contusions or superficial lacerations, no ductal injury
II	Major contusions or lacerations, no ductal injury, no tissue loss
III	Distal transection of the pancreas or a parenchymal injury involving the duct
IV	Proximal transection (to the right of the superior mesenteric vessels) or a parenchymal injury involving the ampulla
V	Massive disruption of the pancreatic head

For multiple injuries, the grade is advanced by one³⁰.

Conclusion

Upper gastrointestinal radiological studies and CT may lead to the diagnosis of blunt duodenal trauma, but exploratory laparotomy remains the ultimate diagnostic test if a high suspicion of duodenal injury continues in the face of absent or equivocal radiographic signs. Most duodenal injuries can be managed successfully by simple repair. More complicated injury requires more sophisticated techniques. High-risk duodenal injury is followed by a high incidence of suture line dehiscence and treatment should involve duodenal diversion. Pancreaticoduodenectomy should be practised only if no alternative is available. Damage control should precede definitive reconstruction. Detailed knowledge of available operative choices and when to use them is important for good overall results.

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Postoperative ileus: a preventable event

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Background: Postoperative ileus has traditionally been accepted as a normal response to tissue injury. No data support any beneficial effect of ileus and indeed it may contribute to delayed recovery and prolonged hospital stay. Efforts should, therefore, be made to reduce such ileus.

Methods: Material was identified from a Medline search of the literature, previous review articles and references cited in original papers. This paper updates knowledge on the pathophysiology and treatment of postoperative ileus.

Results and conclusion: Pathogenesis mainly involves inhibitory neural reflexes and inflammatory mediators released from the site of injury. The most effective method of reducing ileus is thoracic epidural blockade with local anaesthetic. Opioid-sparing analgesic techniques and non-steroidal anti-inflammatory agents also reduce ileus, as does laparoscopic surgery. Of the prokinetic agents only cisapride is proven beneficial; the effect of early enteral feeding remains unclear. However, postoperative ileus may be greatly reduced when all of the above are combined in a multimodal rehabilitation strategy.

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Introduction

Postoperative ileus is generally defined as a transient impairment of bowel motility after abdominal surgery or other injury. Clinically, it is characterized by bowel distension, lack of bowel sounds, and lack of passage of flatus and stool. Symptoms include nausea, vomiting and stomach cramps, and ileus is thus a major contributory factor to postoperative discomfort. Resumption of a regular diet and mobilization is delayed, and hospital stay is thereby prolonged. Ileus has traditionally been accepted as an obligatory physiological response to abdominal surgery, but the purpose of this response in the elective surgical setting has not been established and no data suggest a beneficial effect of the delayed postoperative recovery of gastrointestinal motility. Various pathogenetic mechanisms have been proposed and several pharmacological interventions have been employed to resolve ileus, but so far no single technique or agent has been found effectively to eliminate the problem.

In recent reviews^{1–5} both pathophysiology and pharmacological treatment have been described, but none of these papers has addressed recent advances in perioperative management (including choice of anaesthesia, pain management, nutrition and mobilization) in an integrated

multimodal approach. The present review updates knowledge on the pathophysiology and pharmacological treatment of postoperative ileus, and brings these data into the broader context of a multimodal anaesthetic, analgesic, pharmacological and nutritional rehabilitation strategy in an attempt to reduce ileus and improve postoperative outcome.

Definitions and methods of assessment

Not all segments in the gastrointestinal tract are equally affected by postoperative ileus. The average paralytic state lasts between 0 and 24 h in the small intestine, 24 and 48 h in the stomach, and between 48 and 72 h in the colon after major abdominal surgery. The effective duration of ileus is, therefore, mainly dependent on the return of colonic motility and, in particular, motility of the left colon^{6,7}. Ileus most commonly occurs after intraperitoneal operations, but it may also occur after retroperitoneal and extra-abdominal surgery. The duration is related to the anatomical location of surgery and the longest duration is encountered after operation involving the colon^{8,9}. The difference between right-sided and left-sided colonic procedures on the duration of ileus remains uncertain^{10–12}. In experimental and clinical studies ileus has been

demonstrated to be related to the degree of surgical manipulation and the magnitude of the inflammatory response¹³.

The definition of ileus and methods of assessment are not well defined. As an objective indicator of resolution, assessment of electrical activity has been widely used, focusing on either the return of the migrating myoelectric complex (MMC) or qualitative changes in MMC patterns. However, the MMC reflects mostly fasted state activity and some investigators have found no correlation between return of the MMC or specific MMC pattern and the clinical resolution of postoperative ileus^{6,14}. A correlation between some of the widely used clinical endpoints, such as bowel sounds, passage of flatus and stool, is also controversial. Bowel sounds are non-specific because they may originate in the small bowel as well as in the large bowel, and also require frequent auscultation for assessment. Passage of flatus is highly dependent on reporting by patients, and the correlation between passage of flatus and propulsive bowel movements is unclear⁶. Passage of stool, although manifest as a clinical sign, is not specific, as it may indicate only distal bowel emptying and not necessarily the function of the entire gastrointestinal tract. Other frequently used endpoints include measurements of intraluminal pressure, migration of radio-opaque markers and non-invasive electrical measurements, such as percutaneous registration of electrical activity. Several investigators have found the clinical resolution of ileus to be relatively independent of these technical variables^{15,16}. As no single objective variable has yet been found accurately to predict resolution of ileus, the most adequate definition of resolution probably depends on a combined functional outcome of normalization of food intake and bowel function.

Pathogenesis of postoperative ileus

Inhibitory neural reflexes

Several inhibitory reflexes in the gastrointestinal tract have been proposed to mediate postoperative ileus, including somatovisceral and viscerovisceral reflexes¹. Three anatomically distinguishable reflexes seem to be involved: ultrashort reflexes confined to the wall of the gut, short reflexes involving the prevertebral ganglia, and long reflexes involving the spinal cord. The long reflexes are probably of most importance, since several experimental studies have shown spinal anaesthesia, abdominal sympathectomy and other nerve-cutting techniques to prevent or reduce the development of ileus^{2,3}.

Other experimental studies have demonstrated that selective degradation of splanchnic afferent neurones with capsaicin reduces ileus^{17,18}. This applies to both systemic

administration and direct application at the prevertebral ganglia; perivagal administration is without effect¹⁷. Furthermore, ablation of vagal fibres may not influence gastrointestinal transit after injury in contrast to spinal afferent fibre ablation¹⁷. Several experimental studies suggest that the afferent reflexes originate primarily from the peritoneum and that skin incisions alone, unlike incisions through the peritoneum, do not provoke ileus^{19,20}.

In summary, inhibitory sympathetic reflexes are of major importance in the pathogenesis of ileus. This has substantial clinical implications as these reflexes are subject to modification by epidural blockade.

Neurotransmitters and inflammatory factors

A surgical operation elicits a stress response that is generally considered to be of combined endocrine and inflammatory origin. Although many neurotransmitters and neuropeptides are found locally in the gastrointestinal tract and might possibly contribute to ileus, they may also be released systemically following noxious stimuli or local inflammatory responses (the wound). So far, few comparative studies are available, but plasma changes in motilin and substance P may be related to depressed postoperative gastrointestinal motility²¹. These findings, however, do not exclude the importance of local release of these substances.

Numerous transmitters and peptides are involved in regulating gastrointestinal motility and so may be involved in ileus. Nitric oxide, vasoactive intestinal peptide (VIP) and substance P have been established as inhibitory neurotransmitters in the intrinsic gut nervous system. Experimental studies have shown that VIP and substance P receptor antagonists, as well as inhibitors of nitric oxide synthesis, improve postoperative gastrointestinal transit^{19,22,23}. Induced endotoxaemia in dogs leads to increased concentrations of products of VIP and nitric oxide synthesis combined with decreased gastrointestinal motility^{24,25}. Calcitonin gene-related peptide also inhibits postoperative gastric emptying and gastrointestinal transit, acting on specific peripheral receptors, possibly located in splanchnic afferent nerves or ganglia^{17,26}. Several studies have demonstrated that corticotrophin releasing factor (CRF) is involved in the pathogenesis of ileus, as intracisternal and intraventricular injection of CRF may delay postoperative gastrointestinal transit, which subsequently may be reversed by administration of specific CRF antagonists^{27,28}. Finally, opioids are well established as modulators of transmission in the central and peripheral nervous systems, leading to inhibition of gastric emptying and non-propulsive smooth muscle contraction with an increase in intraluminal pressure throughout the gastrointestinal tract^{29,30}. This effect is predominantly mediated by mu

receptor agonists. Recent experimental studies have shown that selective peripheral kappa agonists may reverse ileus and gut paralysis following surgery or chemical peritonitis^{31–33}. Interestingly, experimental studies have also documented improved visceral pain relief by kappa agonists³².

Little work has focused on the role of local inflammatory responses and cellular events in mediating ileus. Bauer's group has demonstrated, in a series of experimental studies, that the local inflammatory response is related to the extent of surgical trauma and degree of ileus¹³. The effect may be mediated by leucocyte-derived nitric oxide²³, and is prevented by reducing the number of inflammatory cells locally³⁴. Furthermore, the paralytic gut response to surgery seems to be biphasic, consisting of a short temporary initial paralysis, followed by a longer-lasting impairment of muscle activity paralleling the local tissue concentration of inflammatory cells³⁵.

In summary, various neurotransmitters and inflammatory factors are known to be involved in the pathogenesis of postoperative ileus. However, their relative roles, as well as the hierarchical order and cooperation of these substances in the initiation and resolution of ileus, remain obscure.

Perioperative management

Anaesthesia

All anaesthetics used for induction or maintenance of general anaesthesia may depress gastrointestinal motility³⁶. However, the choice of general anaesthetic technique may have insignificant effects on ileus as even prolonged general anaesthesia in surface surgery does not lead to any clinically relevant reduction in bowel motility. The potential contributory effect of nitrous oxide to ileus has been evaluated in several clinical trials comparing nitrous oxide with isoflurane or propofol in abdominal surgery; it has not been found to be of clinical significance^{37–39}. A single dose of neural blockade with spinal or epidural anaesthetic alone or as a supplement to general anaesthesia does not influence the duration of ileus⁴⁰. The role of intraoperative short-acting opioids (alfentanil, remifentanil) on ileus is unknown, but is unlikely to be of clinical significance.

Analgesia

As noted above, it is well established that a surgical noxious stimulus leads to activation of inhibitory sympathetic splanchnic reflexes, and that the choice of analgesic technique may affect several aspects of the surgical stress response, including these inhibitory reflexes⁴⁰. After major

abdominal surgery effective dynamic pain relief may be obtained only by a continuous epidural infusion that includes local anaesthetics⁴¹. Analgesic treatment that includes opioids may prolong ileus, and the use of opioid-sparing analgesia with non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics (balanced analgesia) may reduce ileus.

Epidural analgesia

Theoretically, epidural blockade with local anaesthetics may improve postoperative ileus by several mechanisms: blockade of afferent and efferent inhibitory reflexes, efferent sympathetic blockade with concomitant increase in splanchnic blood flow, and anti-inflammatory effects via systemic absorption of local anaesthetics^{42,43}. Several randomized studies in patients undergoing abdominal procedures have evaluated the effect of epidural thoracic local anaesthetics compared with systemic opioids^{44–51} (*Fig. 1*). Thus, in six of eight studies epidural bupivacaine significantly reduced ileus. In one statistically negative study⁴⁴ the duration of epidural analgesia was only 24 h, whereas in all other studies it was administered for between 48 and 72 h. In the other small, statistically negative study⁵¹ a low thoracic (Th9–12) epidural blockade was used, which may not permit sufficient dermatomal blockade of noxious stimuli to improve gastrointestinal motility.

Compared with epidural opioid or epidural bupivacaine plus low-dose opioid, epidural bupivacaine also led to a reduction in the duration of ileus^{45,50,52,53} (*Fig. 2*). Furthermore, the combination of epidural opioid plus low-dose bupivacaine may also reduce ileus compared with epidural or systemic opioid^{50,53–58} (*Fig. 3*). In one randomized study in hip surgery⁵⁹, the combination of intraoperative plus postoperative lumbar epidural local anaesthetics reduced ileus compared with general anaesthesia plus postoperative intravenously administered analgesia.

The established positive effect of epidural local anaesthetic administration is related to the segmental visceral afferent/efferent blockade which, in abdominal surgery, can be obtained only by thoracic application of the local anaesthetic. Not surprisingly, studies using lumbar or low-thoracic epidural administration of local anaesthetics have not demonstrated the positive effects of epidural analgesia on ileus^{44,51,54,55}.

Experimental studies have shown that local anaesthetics inhibit the development of chemical peritonitis following hydrochloric acid administration⁶⁰ and shorten bowel paralysis after ischaemia⁶¹. However, clinical studies using intraperitoneal or systemic (intravenous) administration of local anaesthetics have been inconclusive with regard to

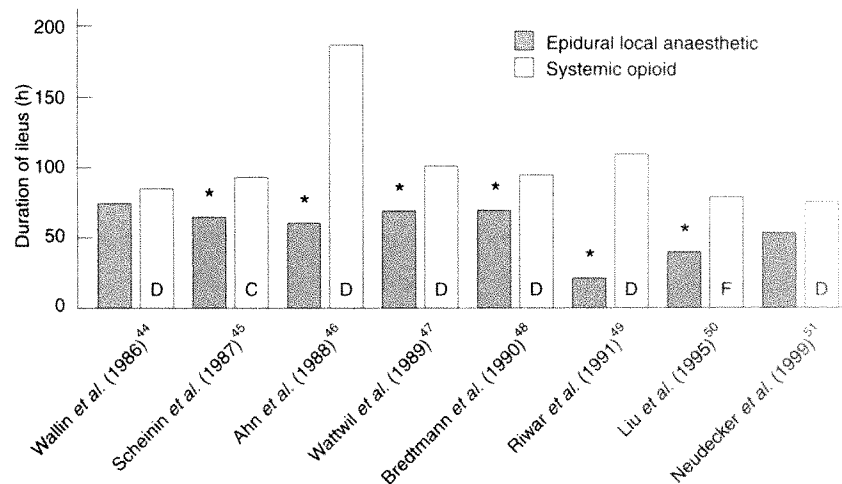


Fig. 1 Randomized clinical trials assessing the effect of epidural local anaesthetic *versus* systemic opioid on postoperative ileus. In all studies colonic surgery was performed, except Wallin *et al.*⁴⁴ (cholecystectomy) and Wattwil *et al.*⁴⁷ (gynaecological surgery). The various endpoints (defaecation (D), combination score (C) and flatus (F)) used to assess resolution of postoperative ileus are indicated. The combination score is defined as a combination of flatus and defaecation. In studies with assessments of both flatus and defaecation, defaecation was given a higher priority than flatus. * $P < 0.05$

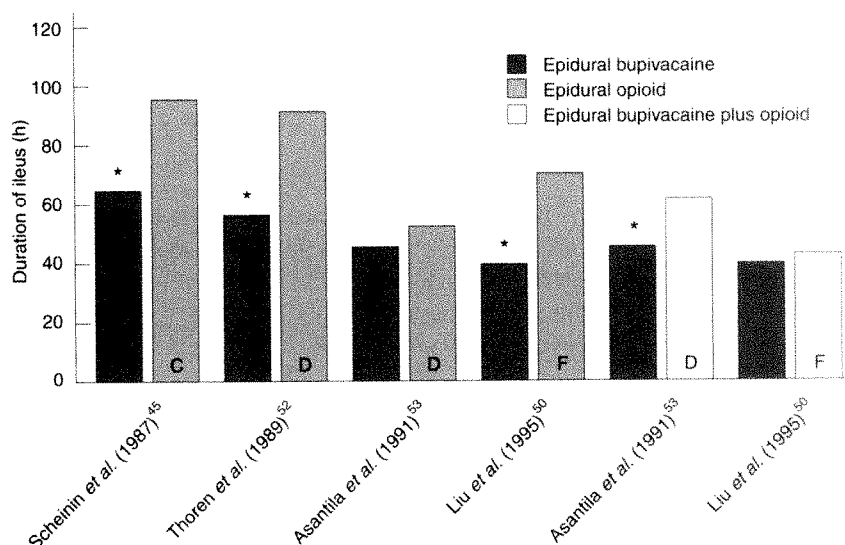


Fig. 2 Randomized clinical trials assessing the effect of epidural local anaesthetic *versus* epidural opioid or epidural local anaesthetic plus opioid on ileus. Two studies^{45,50} were colonic and two studies^{52,53} were gynaecological. The various endpoints (combination score (C), defaecation (D) and flatus (F)) used to assess resolution of ileus are indicated. The combination score is defined as a combination of flatus and defaecation. In studies with assessments of both flatus and defaecation, defaecation was given a higher priority than flatus.

* $P < 0.05$

both analgesic effects⁶² and to any potentially advantageous effect on the resolution of postoperative ileus^{16,62,63}.

Opioid analgesia

It is well known from experimental studies that opioids have a profound inhibitory effect on resting and post-

traumatic gastrointestinal motility^{30,31}. These effects are primarily seen during systemic opioid administration with intravenous patient-controlled analgesia, conventional intramuscular opioid administration or epidural opioid administration^{11,29}. Pain relief apart, there is a major difference between the effects on ileus of these opioid

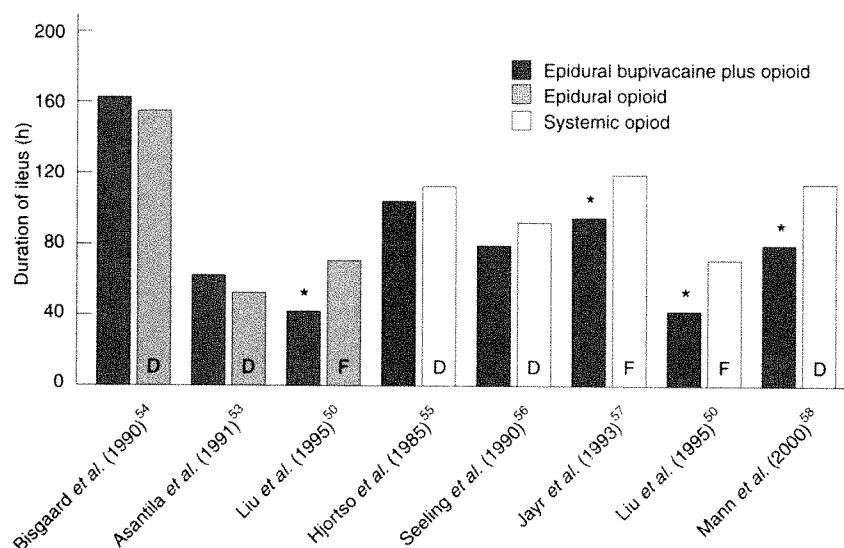


Fig. 3 Randomized clinical trials assessing the effect of a combination of epidural local anaesthetic and opioid *versus* epidural or systemic opioid on ileus. In the studies demonstrating a positive effect of epidural local anaesthetic, thoracic epidural infusion was used. In the remaining four studies, epidural blockade was lumbar or not specified precisely. In all studies except that of Asantila *et al.*⁵³ (hysterectomy), major abdominal (not specified) and/or colonic procedures were performed. The various endpoints (defaecation (D), combination score (C) and flatus (F)) used to assess resolution of ileus are indicated. The combination score is defined as a combination of flatus and defaecation. In studies with assessments of both flatus and defaecation, defaecation was given a higher priority than flatus. * $P < 0.05$

administration techniques and techniques involving local anaesthetics.

Findings from experimental studies demonstrate that kappa opioid agonists may provide sufficient visceral analgesia³² as well as reduce ileus^{31,33}, but this has not been studied in the clinical setting. The effects of a kappa opioid agonist (fedotozine) on pain and bowel function in a non-surgical setting, irritable bowel syndrome, have been negative⁶⁴. Recent studies in chronic methadone users suggest that peripheral opioid antagonists (methylnaltrexone) may reverse the opioid-mediated inhibition of gastrointestinal function⁶⁵, with possible future implications in the surgical setting.

Opioid-sparing analgesia

Based on knowledge of the inhibitory effects of opioids on gut motility, various opioid-sparing analgesic techniques have been developed to avoid the undesirable sequelae of opioid administration in the postoperative period (drowsiness, nausea and vomiting, inhibition of bladder function)⁶⁶. One of the most established techniques of obtaining a 20–30 per cent sparing of opioid is pain relief with NSAIDs⁶⁷. In both experimental and clinical studies, the

administration of NSAIDs and the subsequent opioid-sparing effect has, in most but not all studies, resulted in less nausea and vomiting and improvement in overall gastrointestinal motility^{15,20,68–70}. Similar effects have been obtained with different types of NSAIDs, although no data are available to compare cyclo-oxygenase (COX) 1 *versus* COX-2 inhibitors. The advantageous effect of NSAIDs, apart from the sparing of opioid, may also be related to a direct anti-inflammatory effect mediated by the inhibition of prostaglandin synthesis⁶⁸. The effect of other types of opioid-sparing analgesia (ketamine, paracetamol, tramadol, etc.) has not been finally established.

Nasogastric intubation

The insertion of a nasogastric tube has been the traditional supportive treatment for postoperative ileus, but it does not shorten time to first bowel movement or time to effective oral food intake^{71,72}. Many randomized clinical studies and a meta-analysis have concluded that a nasogastric tube should not be used routinely, and that unnecessary use may contribute to postoperative morbidity such as atelectasis, pneumonia and fever^{71,72}.

Mobilization

Contrary to popular belief, physical exercise does not improve colonic motility in healthy volunteers⁷³. Neither does mobilization of itself shorten the duration of postoperative ileus; recovery of myoelectrical activity is similar in patients mobilized from day 1 compared with day 4 after major abdominal surgery⁷⁴. However, the commonly practised prolonged immobilization after surgery has never been proven to be beneficial⁷⁵. In fact, prolonged bedrest may enhance the risk of postoperative complications and prolong recovery^{41,76}, and so should be avoided for reasons other than recovery of gastrointestinal function.

Early postoperative oral feeding

Food intake elicits a reflex response that is propulsive in action. Several intestinointestinal reflexes connecting various parts of the gastrointestinal tract respond to food intake, producing coordinated propulsive activity⁷⁷. In addition, the presence of food stimulates the secretion of various intestinal hormones, with an overall stimulating effect on gastrointestinal motility⁷⁷.

Traditionally, oral feeding has been delayed after laparotomy until any ileus has resolved clinically. At that

point a liquid diet is administered, gradually progressing to solid food. Patients undergoing major abdominal procedures often have at least 4 or 5 days of semistarvation or total starvation. This is unfortunate because semistarvation contributes to catabolism and so to fatigue and prolonged convalescence⁴¹. Furthermore, several randomized clinical studies have shown that early enteral nutrition may improve immune function and reduce postoperative and post-traumatic infectious complications⁷⁸.

Early uncontrolled studies by Moss⁷⁹ found that ileus was resolved within 48 h when patients received immediate enteral nutrition. Unfortunately, it has been only recently that the traditional restriction of early postoperative oral intake has been questioned seriously; several trials have shown the institution of early enteral feeding both to be safe^{80–86} and to reduce postoperative ileus (Fig. 4). One study of 80 patients undergoing colorectal surgery and randomized to either early enteral feeding or conventional fasting showed that the early fed group tolerated a regular diet 3 days before the later fed group. The former were discharged from hospital 2 days before the traditionally fed group⁸⁸. Another study of 96 gynaecological patients demonstrated that an earlier fed group tolerated solid diet 1 day before a group receiving traditional feeding; the former were discharged 1 day sooner too⁸⁷. Two other studies involving gynaecological patients have similarly demonstrated a reduction in ileus

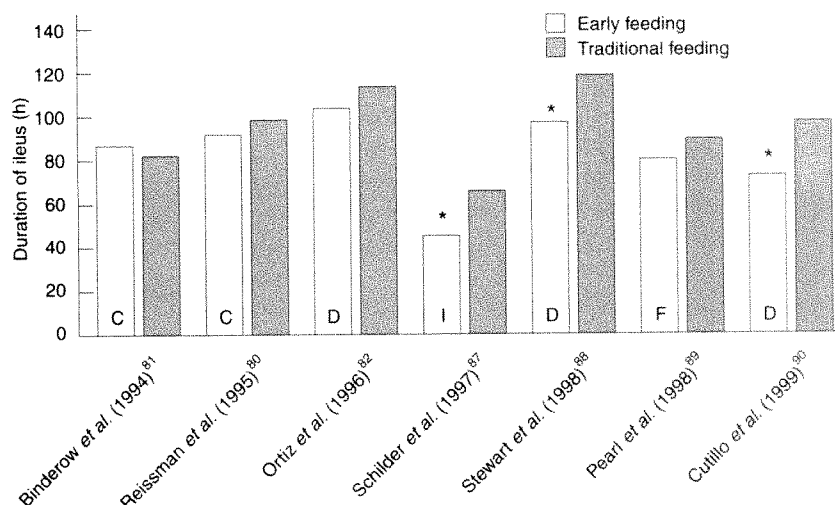


Fig. 4 Randomized clinical trials assessing the effect of early enteral nutrition *versus* traditional feeding (consisting of no oral intake until clinical resolution of ileus or of only liquid oral intake) on resolution of ileus, except Heslin *et al.*⁹¹, which is discussed in the text. Three studies^{87,89,90} were performed in gynaecological patients and the rest in abdominal (not specified or colonic) surgery. As indicators of ileus various endpoints (combination score (C), time to tolerate regular food (I), passage of flatus (F) and defaecation (D)) were used. The combination score is defined as a combination of flatus and defaecation. In studies with assessments of both flatus and defaecation, defaecation was given a higher priority than flatus. * $P < 0.05$

in early fed groups^{89,90}, although in one of these studies⁸⁹ the positive effect was noted in only some of the assessed variables (return of bowel sounds and hospital stay).

In contrast, two other recent trials^{91,92} investigating the effect of early oral feeding have demonstrated no difference in either length of ileus or hospital stay. In one of these studies impairment of pulmonary function and postoperative mobilization with early oral feeding was noted⁹². Of importance, however, in these and other oral feeding studies is that the type of analgesia was rarely reported and, when mentioned, usually consisted solely of opioids and rarely of epidural local anaesthetics^{80–85}. Thus the established stimulatory effect of solid food on intestinal motility may not have been obvious as the profound inhibitory effect of opioids on motility may have dominated. The proven beneficial effects of continuous epidural local anaesthetics, opioid-sparing analgesics and cisapride have unfortunately not been incorporated in previous controlled clinical studies of early enteral nutrition. Future well designed studies are required to evaluate the potential benefits of early enteral nutrition when combined with regimens aimed at early resolution of postoperative ileus.

Laparoscopic surgery

Experimental studies comparing laparoscopic with open cholecystectomy have shown that the laparoscopic approach improves gastric emptying and fasted state gastrointestinal motility^{14,93}. However, ileus is clinically non-existent after laparoscopic cholecystectomy⁹⁴ and so these results are not applicable to major abdominal procedures. In experimental studies in colonic surgery, the laparoscopic technique leads to earlier return of gastrointestinal motility as well as earlier normalization of myoelectrical activity and bowel movement compared with open colectomy^{95,96}. The mechanisms involved may include reduced activation of inhibitory reflexes and local inflammation due to a reduction in surgical trauma¹³.

In clinical studies, earlier resolution of ileus has been demonstrated following laparoscopic colonic surgery. Four prospective randomized clinical studies comparing laparoscopic and open colonic techniques have shown a reduction in postoperative ileus with the laparoscopic method in two of three studies in which it was assessed^{97–99} (Fig. 5). However, in a broader context the difference between laparoscopic and conventional abdominal surgery with respect to ileus remains to be clarified; expectations may have led to treatment bias favouring earlier food intake and less routine use of nasogastric tubes in laparoscopic groups.

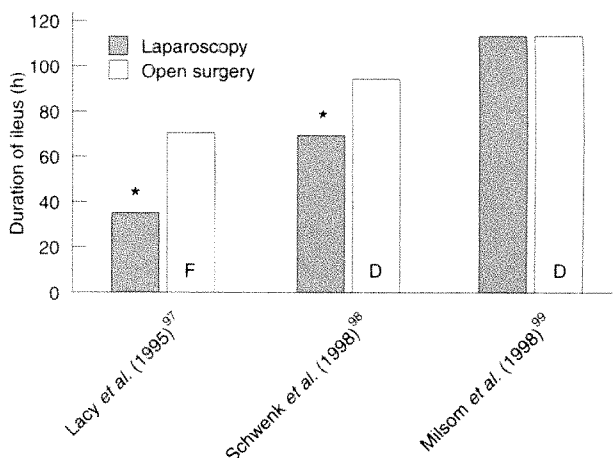


Fig. 5 Randomized clinical trials comparing the effect of laparoscopic *versus* open colonic surgery on ileus. F=flatus, D=defaecation. * $P < 0.05$

Prokinetic agents

Cisapride

Cisapride enhances acetylcholine release from the intrinsic plexus and acts as a serotonin receptor agonist; it may stimulate all aspects of gastrointestinal motility¹⁰⁰. Nine randomized controlled clinical trials have been performed on postoperative patients^{101–109} (Fig. 6). In one study, however, patients (neonates) were included only after an initial 10-day period of ileus¹⁰⁹. In four studies cisapride significantly reduced ileus; it was administered intravenously in three of them. In one of these studies¹⁰⁷ 43 per cent of patients undergoing various abdominal operations had flatus 2 h after the intravenous administration of cisapride 4 mg, compared with 12 per cent in the control group. In another study on postoperative patients¹⁰⁸ 55 per cent had flatus 4 h after the intravenous administration of cisapride 8 mg, compared with 29 per cent of patients receiving placebo. In only one clinical trial¹⁰⁵ was cisapride administered orally; ileus was reduced from 4.8 to 3.7 days. In three of the four remaining (negative) studies, cisapride was administered rectally. These results suggest that the beneficial effect of cisapride on ileus depends on the route of its administration, favouring intravenous or, possibly, oral administration in the postoperative period. However, adverse cardiac effects may occur with cisapride, which may therefore be contraindicated in high-risk patients¹¹⁰.

Ceruletide

Ceruletide is a synthetic peptide whose cholecystokinin antagonist activity may stimulate gastrointestinal motility.

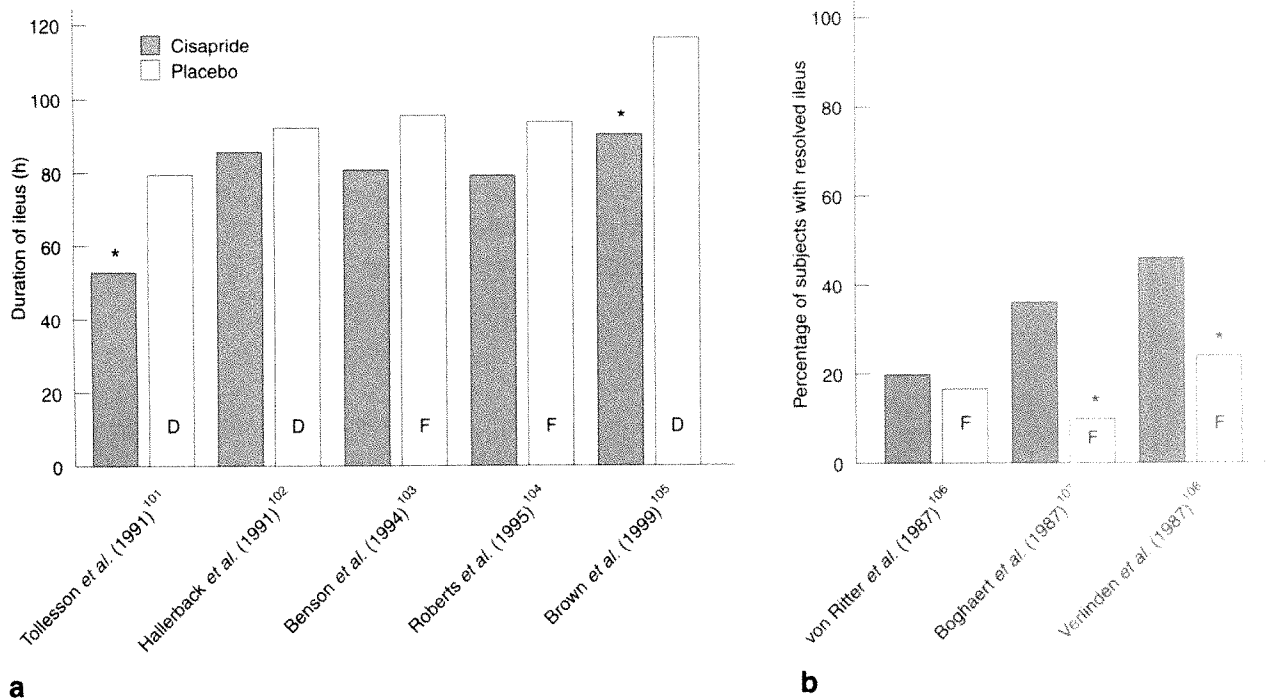


Fig. 6 Randomized clinical trials evaluating the effect of cisapride on **a** duration of ileus and **b** percentage of subjects with resolved ileus. Various indicators of postoperative ileus (flatus (F) and defaecation (D)) and were used as well as various doses of drug (4–30 mg administered for between 1 and 7 days) and various routes of administration (intravenous, rectal and oral). In all studies, patients underwent various abdominal (not specified) or colonic procedures. In studies with assessments of both flatus and defaecation, defaecation was given a higher priority than flatus. * $P < 0.05$

In two clinical placebo-controlled studies ceruletide has been found to reduce ileus slightly^{111,112}. However, side-effects such as nausea and vomiting, which may require additional antiemetic treatment, limit the potential use of ceruletide. Further studies are necessary on other cholecystokinin antagonists before clinical recommendations can be made.

Erythromycin

Erythromycin stimulates the motilin receptor and so may induce a MMC. However, the only existing prospective clinical randomized study found no effect of postoperatively administered erythromycin on ileus after abdominal surgery¹¹³.

Metoclopramide

Metoclopramide may potentially influence gastrointestinal motility by acting as a dopamine antagonist, as well as by direct and indirect effects on cholinergic and serotonergic receptors throughout the gastrointestinal tract. Six con-

trolled clinical studies exist in patients undergoing abdominal surgery to assess the effect of metoclopramide on ileus. In three of the studies endpoints such as bowel sounds, food intake and defaecation were assessed^{114–116} (Fig. 7). Of the remaining three studies, one assessed ileus with a functional combination score¹¹⁷. In another¹¹⁸, the study population was divided according to the median drug dose received, and in the third study¹¹⁹ the number of patients with bowel sounds in each group was counted after 2 days. Despite the variety of endpoints, none of these studies has demonstrated a significant effect of metoclopramide on the resolution of postoperative ileus.

Somatostatin

Somatostatin is known to inhibit the secretion of gastrointestinal hormones. In experimental studies the somatostatin analogue, octreotide, has been shown to enhance colonic transit and to restore interdigestive myoelectrical complexes^{21,120}. The effect of somatostatin analogues on postoperative ileus has not been investigated in clinical studies.

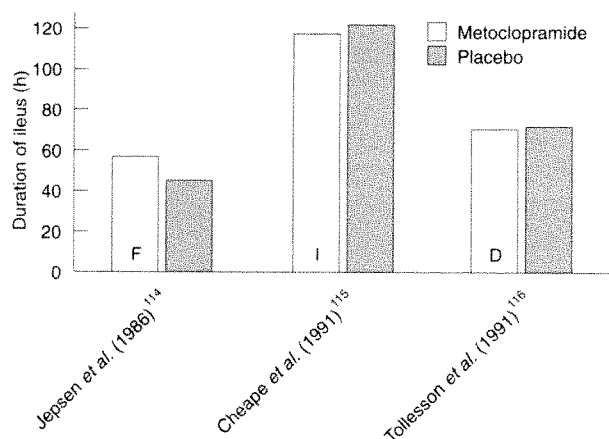


Fig. 7 Effect of metoclopramide on ileus. Three of the existing six clinical trials are shown. The remaining three studies are discussed only in the text, owing to the great variety of endpoints assessed and statistical analyses. Surgery was aortic¹¹⁴, various abdominal¹¹⁵ or cholecystectomy¹¹⁶. Indicators of ileus were flatus (F), time to solid food intake (I) and defaecation (D)

Adrenoblockers

Although inhibitory reflexes mediated by sympathetic visceral afferents are important in the development of ileus, the effect of adrenoblocking agents in reducing ileus in the clinical setting has been rather limited^{121,122}. It is probably clinically insignificant.

Laxatives

Despite the wide use of laxatives with prokinetic effect in non-surgical patients, no randomized clinical study exists to assess the possible beneficial effect of postoperative laxatives on ileus. In fact only one clinical study (unblinded and non-randomized) has assessed the effect of postoperatively administered laxatives (magnesia and biscolic suppositories) and this was in 20 consecutive gynaecological patients¹²³. The duration of ileus in the treated group (time to flatus and bowel movement) was 3 days. Furthermore a 50 per cent reduction in length of hospital stay (4 *versus* 8 days) was noted.

Conclusion

Several prokinetic drugs are available, but so far none has been found effective in the elimination or reduction of postoperative ileus, with the exception of cisapride. However, as a sole agent, cisapride is likely to be of limited clinical relevance, although it may be useful in conjunction with other techniques.

The future

In the future we must consider a multimodal concept of controlling perioperative pathophysiology, postoperative ileus and rehabilitation. The pathogenesis of ileus involves mainly inhibitory neural reflexes, and inflammatory mediators and neurotransmitters from the site of intestinal injury. Effective pain relief with continuous thoracic epidural local anaesthetics is the most important method of reducing ileus. It appears that several techniques, when studied individually, may reduce the duration of ileus without eliminating the problem. A rational treatment would therefore be a combination of avoidance of the routine use of nasogastric tubes, the use of a continuous thoracic epidural local anaesthetic regimen for at least 48 h, the use of additional opioid-sparing analgesia, and routine early oral nutrition. Other additional methods may be supportive, for instance cisapride and the use of a laparoscopic technique. Unfortunately, no randomized studies are available to document the validity of this multimodal concept, but several case series suggest that such an approach may significantly reduce, or even eliminate, ileus after colonic surgery.

Sixty consecutive patients scheduled for elective open colorectal surgery participated in an accelerated rehabilitation programme. Their median age was 74 years and 33 per cent were American Society of Anesthesiologists grade III or IV. Analgesia consisted of continuous thoracic epidural blockade with local anaesthetics over 48 h, combined with systemic paracetamol and ketorolac. Nasogastric tubes were removed immediately after surgery and oral food intake was started on the day of operation. The patients were mobilized within 8 h of surgery. The median hospital stay of these unselected patients was 2 days and ileus was considered to be significantly reduced, as 95 per cent of the patients tolerated normal food and had defaecation within 48 h of operation^{124,125}. Similar results have been found in a group of 17 patients undergoing elective colonic surgery; 12 passed stool within 48 h, despite the fact that several patients received morphine after operation¹²⁶. Thirty-nine patients undergoing laparoscopic colonic surgery participated in a similar programme and 35 had normal bowel function on day 2 after operation^{127,128}. The combination of epidural anaesthesia and analgesia and of a standardized care protocol has also been found to reduce the duration of postoperative ileus and hospital stay by 1 day, compared with other analgesic techniques, in patients undergoing elective colorectal surgery^{50,129}.

In conclusion, these preliminary findings suggest that a multimodal rehabilitation approach may result in a major improvement in terms of early resolution of postoperative ileus. Further trials are needed to document efficacy with

respect to different types of operation, safety and the potential for reducing overall postoperative morbidity and cost.

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Operative treatment of pseudocysts in patients with chronic pancreatitis

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Background: Pseudocysts associated with chronic pancreatitis are generally intrapancreatic and associated with parenchymal disease. They tend to persist and cause complications. Minimally invasive methods of treatment challenge the traditional techniques of operative management. Surgical operation allows definitive treatment of the pseudocyst with the option of dealing appropriately with the diseased pancreas and excluding a neoplastic process. The aim of this study was to review the safety and efficacy of a surgical approach to the management of pseudocysts associated with chronic pancreatitis.

Methods: A personal series of 112 consecutive patients operated for pseudocysts in the setting of chronic pancreatitis was reviewed. Chronic pancreatitis was confirmed by imaging studies in association with exocrine and/or endocrine failure. Cysts were multiple in 31 patients and presented with complications other than pain in 47. Data were collected prospectively regarding the clinical presentation, the nature of the operation and its outcome.

Results: Forty-eight patients (43 per cent) underwent drainage procedures, 56 (50 per cent) had a resection and eight (7 per cent) had a combination. Larger cysts and those located in the head and neck tended to be drained, while smaller and distal cysts were more often resected. The morbidity rate was 28 per cent and the operative mortality rate was 1 per cent. The cyst recurrence rate was 3 per cent and pain was relieved in 74 per cent of patients.

Conclusion: Operative management of pseudocysts associated with chronic pancreatitis is effective with low morbidity and mortality rates. The introduction of newer minimally invasive techniques will have to withstand comparison to this traditional approach.

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Introduction

The pseudocysts that follow an attack of acute pancreatitis will often resolve spontaneously, but the chronic cysts that develop in association with permanent changes in the pancreas (i.e. chronic pancreatitis) generally persist and may give rise to pain or complications¹. Although operative treatment has previously held sway, several non-operative alternatives are now available for the management of pancreatic pseudocysts associated with chronic pancreatitis. Aspiration and drainage of uncomplicated pseudocysts may be performed percutaneously under ultrasonographic or computed tomography (CT) guidance². Pseudocysts situated adjacent to the duodenum or stomach can be drained internally using diathermy to create a fistula during endoscopy³. Internal drainage has also been accomplished with the minimally invasive techniques of laparoscopic⁴ and percutaneous^{5–8} transgastric pancreatic cystgastrostomy.

These innovative techniques challenge the traditional operative approach to pancreatic pseudocysts, yet the results of operative management have been excellent, with low morbidity, mortality and recurrence rates^{9–12}. The operative approach is versatile, allowing wide and permanent internal decompression of larger cysts and resection of smaller cysts, together with the underlying segment of diseased pancreas, as necessary¹. This paper evaluates a personal consecutive series of 112 patients who underwent surgical treatment for pseudocysts in the setting of established chronic pancreatitis.

Patients and methods

Prospective data were recorded on 112 patients undergoing open operation for pseudocysts associated with chronic pancreatitis between 1979 and 1998. There were 84 men (75 per cent) and 28 women with a mean age of 44 (range

15–80) years. All patients had established chronic pancreatitis as a result of alcoholism ($n = 80$), recurrent attacks of acute pancreatitis ($n = 6$), cholelithiasis ($n = 5$) or unknown causes ($n = 21$). All operations were performed or supervised by the senior author.

A previously published algorithm for the management of chronic pancreatitis¹ forms the basis of this series. Preoperative imaging included ultrasonography, CT, endoscopic retrograde cholangiopancreatography (ERCP) and angiography and was frequently supplemented by operative ductography or cystography. These techniques were used to provide information on the size, location and number of cysts, the extent of pancreatic parenchymal disease, the nature of the main pancreatic duct and its relationship to the cyst and finally the presence of portal hypertension, venous occlusion, arterial anomalies and pseudoaneurysms.

All patients presented with abdominal pain. Additional complications directly related to the cyst occurred in 47 of them (42 per cent): jaundice ($n = 18$), infection ($n = 9$), pancreatic abscess ($n = 9$), gastric outlet obstruction ($n = 9$), haemorrhage ($n = 6$), persistent fistula secondary to percutaneous drainage ($n = 5$), cyst rupture ($n = 2$), pancreatic ascites ($n = 2$), pleural effusion ($n = 1$) and splenic infarction as a result of pseudoaneurysm ($n = 1$) (Fig. 1).

All patients had unequivocal evidence of chronic pancreatitis with corresponding structural and/or functional abnormalities. Patients who developed pseudocysts after episodes of acute pancreatitis (as defined by the Atlanta criteria¹³) without pre-existing pancreatic disease were not included in this series. A total of 49 patients (44 per cent) had undergone previous cyst drainage or other operative procedures directed at the pancreatitis, mostly at other hospitals, as follows: 19 operative, 17 percutaneous (Fig. 2), four endoscopic, one embolization and eight more than one method. Nineteen patients had had multiple procedures (Table 1).

Follow-up was carried out via the outpatient clinic for recently treated patients, or by telephone and letter to the patient or general practitioner for those who were treated in earlier years. Information was collected regarding the patient's pain, insulin requirement, pancreatic enzyme supplementation, any additional treatment for pseudocysts and overall satisfaction with the outcome of the operation.

Results

Cyst features

A total of 147 cysts was treated in 112 patients. The mean cyst diameter was 7.2 (range 2–30) cm and multiple cysts occurred in 31 patients (28 per cent). Eighty-one patients

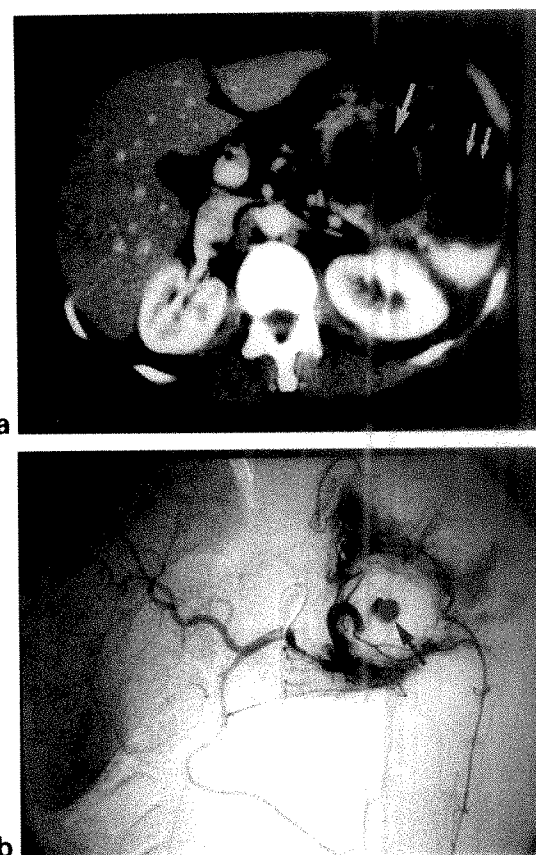


Fig. 1 A 41-year-old man with chronic alcoholic pancreatitis was admitted with haematemesis and abdominal pain, and gastroscopy showed an ulcer on the greater curve of the stomach. Computed tomography (a) showed two apparent pseudocysts related to the distal pancreas; the medial 'cyst' (single arrow) was an arterialized haematoma while the lateral 'cyst' (double arrow) was an abscess cavity involving an infarcted spleen. Arteriography (b) showed abrupt termination of the splenic artery with extravasation of contrast (arrow) into a spherical haematoma

presented with a single cyst, 27 patients had two cysts and four patients had three cysts. Cysts were classified according to size (Table 2) and were intrapancreatic in 90 patients (80 per cent), extrapancreatic in seven (6 per cent) and a mixture in 15 patients. Among patients with intrapancreatic cysts, the distribution was relatively even between the right ($n = 44$) and left ($n = 36$) sides of the gland; ten were bilateral.

The pancreatic duct was imaged in 91 patients (81 per cent); ERCP alone was performed in 44 patients and operative pancreatography alone in 18, while 29 patients underwent both investigations. This imaging demonstrated pancreatic duct dilatation in 23 patients and communication between the cyst and the main pancreatic duct in 34 (37 per cent) of 91 patients. A common bile duct stricture was demonstrated in 17 patients. Angiography was performed in



Fig. 2 Computed tomogram showing a chronic pseudocyst in the distal pancreas that failed to resolve despite prolonged percutaneous drainage. Operation was indicated for a persistent external fistula

Table 1 Pancreatobiliary procedures performed before referral

	No. of procedures
Percutaneous	
Aspiration	23
Drainage	5
Cystgastrostomy	3
Coeliac plexus block	1
Arterial embolization	1
Paracentesis	1
Pleural aspiration	1
PTC drain	1
Endoscopic	
Biliary stent	2
Pancreatic stent	1
Sphincterotomy	1
Cystgastrostomy	1
Diagnostic laparoscopy	1
Operative	
Cholecystectomy	10
Cystgastrostomy	6
Distal pancreatectomy	5
External cyst drainage	3
Cystjejunostomy	2
ECBD, T tube	2
Gastroenterostomy	1
Cyst aspiration	1
Sphincteroplasty	1

Forty-nine patients had at least one procedure and 19 patients more than one. PTC, percutaneous transhepatic cholangiography; ECBD, exploration of the common bile duct

87 patients (78 per cent), showing splenic vein thrombosis in 24, portomesenteric thrombosis in four, combined splenic and portomesenteric thrombosis in three, pseudoaneurysm of the splenic artery in three and a combination of pseudoaneurysm and venous thrombosis in a further three patients. In patients undergoing angiography, the yield of

Table 2 Surgical procedures according to size of pseudocyst

Size (cm)	Resection	Drainage	Combined*	Total
<5	23	15	6	44
5–10	37	41	5	83
>10	5	14	1	20
Total	65	70	12	147

*Combination of a resection and drainage procedure

venous or arterial pathology (not including anatomical information) was 43 per cent (37 of 87). Portal hypertension was evident in 22 patients, of whom 16 underwent resection. In patients with right-sided portal hypertension, drainage procedures were performed. In those with splenic vein thrombosis and a left-sided cyst, distal resection with splenectomy was preferred.

Operative procedures

A drainage procedure was performed in 48 patients (43 per cent) and a resection was carried out in 56 patients (50 per cent). Eight patients (7 per cent) underwent a combination of both procedures. The mean operative time was 4.6 (range 1.5–9.5) h. Patients with one or more cysts located solely to the right of the portal vein more frequently underwent some form of drainage procedure than those with cysts solely to the left of the portal vein (26 *versus* 13), while left-sided cysts were more often treated by resection (31 *versus* 22). Of the 14 patients with bilateral cysts, nine received drainage alone, three had resection alone and two had a combination of both. Resection was generally preferred to drainage for smaller cysts (mean size 6.3 *versus* 8.3 cm).

Drainage

Cystjejunostomy using a retrocolic Roux-en-Y loop was undertaken in 43 patients and cystduodenostomy in only two patients. The same Roux loop was used to drain the bile duct in patients with a history of jaundice or cholangitis ($n = 7$), or a dilated main pancreatic duct in the form of a longitudinal pancreaticojejunostomy (LPJ) ($n = 18$) or additional cysts ($n = 17$). Other operative procedures included cholecystectomy ($n = 18$), splenectomy ($n = 2$), distal pancreatectomy ($n = 1$), bile duct exploration ($n = 1$) and feeding jejunostomy ($n = 1$). Four patients with infected or extrapancreatic pseudocysts were considered suitable only for deroofting and external drainage, rather than formal anastomosis.

Resection

Pancreatic resection consisted of distal pancreatectomy ($n = 33$), proximal pancreatectomy ($n = 16$) or total pancrea-

tectomy ($n=7$). The specific indications for resection included haemorrhage ($n=6$; four due to pseudoaneurysm), bile duct obstruction ($n=9$), duodenal obstruction ($n=4$), infection ($n=4$), persistent fistula following percutaneous drainage ($n=2$) and suspicion of malignancy ($n=2$). Many patients (26 of 39) whose operation included distal pancreatectomy had concomitant splenectomy, which was necessitated by splenic vein thrombosis ($n=14$) or encasement of the splenic vessels within the inflammatory scar tissue. Six patients with a pseudocyst densely adherent to posterior abdominal structures had part of the cyst wall left behind after resection. Additional procedures in this group included cholecystectomy ($n=5$), LPJ ($n=3$) and choledochojejunostomy ($n=1$).

Pylorus-preserving proximal pancreatoduodenectomy was performed in 15 patients and Whipple's operation in one patient with duodenal scarring. In eight patients the pseudocyst was causing bile duct or duodenal obstruction. In six patients a small portion of the cyst wall was left *in situ* to protect the portal vein. Three patients had concomitant cholecystectomy and two had LPJ. Total pancreatectomy was performed *de novo* in six patients and as a completion procedure in one patient with recurrent cysts following previous distal resection. The pylorus was preserved in four patients and the spleen in two.

Morbidity and mortality rates

There was one postoperative death in this series (1 per cent). A 66-year-old man with chronic alcoholic pancreatitis underwent cystjejunostomy plus LPJ and cholecystectomy for an infected pseudocyst in the neck of the pancreas. He subsequently required relaparotomy for anastomotic dehiscence and then again for secondary haemorrhage. The bleeding was controlled, but he died from multiple organ failure. A total of 48 postoperative complications developed in 31 patients (28 per cent). Reactive haemorrhage complicated three drainage procedures and three pancreatic resections (two distal, one proximal). Another patient bled from a gastric ulcer. Six of these seven patients required reoperation. Postoperative haemorrhage was not related to portal hypertension. Other complications were chest infection ($n=11$), intra-abdominal abscess ($n=11$), enteric or pancreatic fistula ($n=6$), wound infection ($n=4$), transient jaundice ($n=3$), transient bile leak ($n=2$), central line sepsis ($n=2$), pseudomembranous colitis ($n=1$) and stroke ($n=1$). Complications followed total resection in three of seven patients, distal resection in 12 of 33 patients, drainage procedures in 14 of 48 patients, combination procedures in one of eight patients and proximal resection in one of 16 patients. Late death followed in 12 patients (11 per cent) at a mean of 4.8 (range 0.7–9.6) years after operation.

Outcome

Three 'cysts' recurred (3 per cent), each at about 12 months. One arose in a different part of the pancreas following cystjejunostomy and was treated with a distal resection. The other two developed in the 'pancreatic bed' after distal pancreatectomy and probably represented old collections of blood or pancreatic juice; each was treated successfully with percutaneous drainage. Excluding patients who underwent total pancreatectomy, and in those with adequate data, 26 (33 per cent) of 78 patients developed insulin-dependent diabetes during follow-up. Five patients developed diabetes within 6 months of operation; all of these had undergone distal resection. Excluding the early postoperative death (1 per cent) and using the available assessment in those who subsequently died, 74 per cent of patients (82 of 111) were pain-free and 82 per cent (91 of 111) were satisfied with their operative treatment.

Discussion

The operative management of chronic pancreatic pseudocysts aims to obliterate the cyst either by resection or drainage, thereby preventing the serious complications of cyst rupture, haemorrhage, infection and biliary or duodenal obstruction, and hopefully ridding the patient of the invariable pain^{9,14–16}. In the present series these goals were achieved successfully with a low rate of serious complications and a low recurrence rate.

The reported incidence of pseudocysts in chronic pancreatitis varies from 11 to 60 per cent^{15,17–19}. Many authors discuss pseudocysts associated with acute pancreatitis together with those occurring in the setting of chronic pancreatitis, yet these clearly have a different natural history¹⁴. Grouping them together makes it difficult to interpret management plans and outcomes^{1,20}. The operative results in this series—mortality rate 1 per cent, morbidity rate 28 per cent and cyst recurrence rate 3 per cent—together with the lack of spontaneous resolution and the risks of delaying operation justify an aggressive surgical policy. These are difficult operations requiring a degree of expertise, with reported mortality rates of 13 per cent¹¹ and morbidity rates of 50 per cent¹⁷.

Pseudocyst size (more than 4 cm) and an extrapancreatic position have been shown to be independent predictive factors for persisting symptoms and complications^{10,21}. Also, pseudocysts present for more than 6 weeks seldom resolve spontaneously, and the incidence of complications correlates with their age^{14,22}. The incidence of complications in chronic pancreatic pseudocysts was 42 per cent in the present series but can be as high as 55 per cent¹⁵. Thus for most pseudocysts associated with chronic pancreatitis,

the best time for intervention is upon diagnosis, in the confident expectation of finding a mature cyst capable of holding sutures^{11,14,23–25}. However, infected pseudocysts should be drained externally by non-operative techniques unless the cyst is enormous, multiloculated or contains highly viscid pus^{26,27}, in which case operative external drainage is usually required.

Ductal communication was detected in 34 (37 per cent) of 91 patients in whom the duct was imaged, while other series have reported rates from 33 to 54 per cent^{28,29}. Magnetic resonance pancreatography has recently become available and may prove a useful substitute to ERCP. As previously reported^{11,27,30}, the demonstration of ductal dilatation led to drainage of the main pancreatic duct in addition to definitive treatment of the pseudocyst in 18 patients, thereby treating the entire disease process and not just the cyst. By showing duct–cyst communication, preoperative ERCP can be used to refine the operative plan³¹ and reduce the likelihood of an adverse outcome³².

Visceral angiography was performed in 87 patients (78 per cent) in the present study, demonstrating important vascular lesions in 37 patients (43 per cent): six pseudoaneurysms and 34 cases of major venous involvement. Although other techniques (spiral CT, duplex imaging, endoscopic ultrasonography, magnetic resonance angiography) can give useful information, routine angiography continues to be valuable in patients with chronic pancreatic pseudocyst disease.

The choice of operative procedure depends on the size and location of the pseudocyst, any complications and the severity of the underlying chronic pancreatitis. A balance must be reached between adequate treatment of the diseased segment (pseudocyst) and retention of functioning pancreatic tissue³³. The pseudocysts of chronic pancreatitis are generally intrapancreatic (94 per cent in this series) and are associated with a patent lesser sac, which is an important consideration for those contemplating endoscopic or percutaneous cystgastrostomy. With a complication rate of 24–50 per cent^{11,34} and a recurrence rate of 20–30 per cent³⁵, external drainage is rarely warranted in the elective situation^{11,36}. Cystjejunostomy with a Roux-en-Y loop was performed almost exclusively as the procedure of choice for internal drainage in the present series (43 of 45). In 29 patients the Roux loop was also used for a secondary purpose.

In this series, pancreatic resection was performed more commonly than drainage. Resection was generally preferred for smaller cysts, especially those located in the body or tail of pancreas, also for complicated cysts and when there was suspicion of malignancy. Small pseudocysts in the head of pancreas contributing to bile duct or duodenal obstruction may be incorporated in a pancreatoduodenectomy, but pseudocysts in the head or neck may compress the superior

mesenteric artery or portal vein, thus increasing the risk of vascular injury during resection.

The cyst recurrence rate in this series was only 3 per cent, but higher rates have been reported²⁹. Most often recurrent cysts represent progressive disease in the remaining gland rather than a failure of the previous treatment. A late mortality rate of up to 15 per cent has been reported by others^{11,29} and arises from a variety of causes. There was no significant pattern to the late deaths in the present series.

Pain relief is an important objective in the management of patients with chronic pancreatitis but one of the most difficult to assess. Successful pain relief after operative management of pseudocysts associated with chronic pancreatitis is reported at 25–86 per cent^{16,37,38}, while a rate of 74 per cent was achieved here. This wide range is explained first by the duration of follow-up (which can be difficult in this group^{11,14,39}) and second by the representation of alcohol as an aetiological factor in the series. Studies with a low proportion of alcoholics and with short follow-up tend to have better results, but sustained pain relief can be anticipated in about 60 per cent of patients overall⁴⁰.

Despite the proliferation of modern, 'minimally invasive' techniques for dealing with pancreatic pseudocysts, there remains a clear role for operative treatment in patients with established chronic pancreatitis. It permits definitive treatment of the pseudocyst and underlying disease by allowing concomitant drainage of a dilated main pancreatic duct or obstructed common bile duct and resection of adjacent unhealthy gland. Endoscopic drainage is limited to pseudocysts in favourable positions and may be hazardous in patients with intrapancreatic pseudocysts and those with a patent lesser sac. Percutaneous drainage risks chronic cutaneous fistula formation and secondary infection of the pseudocyst cavity. Both methods have the additional risk of mistreating cystic neoplasms masquerading as a pseudocyst^{41,42}.

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Surgical treatment of adult primary hepatic sarcoma

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Background: Primary sarcomas of the liver are extremely rare in adults. Optimal therapeutic approaches remain unclear.

Methods: Twenty consecutive adult patients who had surgical treatment for primary hepatic sarcomas were reviewed. Patient age ranged from 23 to 80 years. Other than one patient with primary hepatic angiosarcoma who had a history of thorium dioxide colloid (Thorotrast) exposure 23 years before diagnosis, no predisposing causes were apparent. Nineteen patients had hepatic resection and one patient had an orthotopic liver transplant. No patient received neoadjuvant chemotherapy or radiotherapy but radiotherapy was delivered intraoperatively in one patient.

Results: Leiomyosarcoma was the most common histological type of sarcoma diagnosed (five of 20 patients), followed by malignant solitary fibrous tumour (four) and epithelioid haemangioendothelioma (three). Fourteen tumours were high-grade sarcomas and six were low grade malignancies. Thirteen patients developed a recurrence. Distant metastases (ten patients) and intrahepatic recurrence (six) were the predominant sites of initial treatment failure. Six patients received salvage chemotherapy. Histological grade was the only factor significantly associated with overall patient survival ($P=0.03$). With complete resection, patients with high-grade tumours had a 5-year survival rate of 18 (95 per cent confidence interval 5–62) per cent compared with 80 (52–100) per cent for patients with low-grade tumours. The 5-year survival rate for all 20 patients was 37 (20–60) per cent.

Conclusion: Surgical resection is the only effective therapy for primary hepatic sarcomas at present. Better adjuvant therapy is necessary, especially for high-grade malignancies, owing to the high failure rate with operation alone.

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Introduction

Primary sarcomas of the liver are extremely rare in adults¹ and only slightly more common in children², representing approximately 0.1 per cent of primary malignant neoplasms of the liver^{3,4}. There are no distinct clinical characteristics that allow the diagnosis of hepatic sarcoma to be made solely on the basis of history, physical examination and imaging studies. Sarcomas metastatic to the liver from other sites need to be distinguished from primary hepatic sarcomas. Because of their rarity, the clinicopathological determinants of survival as well as the optimal therapeutic approaches remain unclear for primary hepatic sarcomas.

Keating and Taylor⁵ reported in 1985 that angiosarcoma

was the most common type of primary hepatic sarcoma representing 36 per cent of the total followed by leiomyosarcoma (12 per cent) and fibrosarcoma (7 per cent). Previous reports have described a total of 17 patients with primary hepatic malignant fibrous histiocytoma (reclassified as malignant solitary fibrous tumour), 36 patients with fibrosarcoma and 31 patients with leiomyosarcoma^{6–10}.

Herein, results are reported for the surgical treatment of 20 consecutive adult patients with primary hepatic sarcoma. The literature on this topic has also been reviewed and, after evaluating the present experience, a treatment plan for these tumours is proposed.

Patients and methods

Between 1979 and 1996, 20 adult patients (aged over 18 years) with the diagnosis of a primary hepatic sarcoma

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Immunohistochemical staining

Antibody	Tumours commonly positive for stain	No. of tumours tested	No. of positive tumours
BerH2(CD30)	Lymphoma	1	0
LCA(CD45)	Lymphoma	1	0
CD31	Angiosarcoma	2	1
CD34	Angiosarcoma, solitary fibrous tumour	3	2
Wide-spectrum keratin	Carcinoma	5	0
CAM 5-2	Carcinoma	1	0
Keratin AE1/AE3	Carcinoma	4	0
CEA	Adenocarcinoma	1	0
EMA	Carcinoma	1	0
S-100	Melanoma	3	0
HMB-45	Melanoma	2	0
Synaptophysin	Neuroendocrine tumours (carcinoid)	1	0
Vimentin	Sarcoma	8	8
Smooth muscle actin	Leiomyosarcoma	10	2
Desmin	Rhabdomyosarcoma		
	Leiomyosarcoma	9	0
Factor VIII	Angiosarcoma	4	2

CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen

were treated. All clinic records were reviewed and complete follow-up assured. All laboratory, radiological, surgical and pathological reports were reviewed. The clinical reports were scrutinized for specific diagnostic and therapeutic information. The presence of lung metastases was evaluated by chest radiograph or computed tomography (CT) reports. Ultrasonographic and CT scans were reviewed to determine site, size and number of the primary hepatic sarcoma, as well as the presence of vascular invasion and distant intra-abdominal metastases. Patients with evidence of, or a previous history of extrahepatic abdominal, retroperitoneal or soft tissue sarcomas were excluded.

The histopathology of all tumours was confirmed separately by two pathologists. All tissue blocks available for study were reviewed. The sarcomas were reclassified according to current histological criteria for soft tissue sarcoma¹¹. In 11 patients, the immunohistochemical stains shown in *Table 1* were used to finalize a specific diagnosis when histological features alone were insufficient. The pathological features used to distinguish primary from secondary hepatic sarcoma were carefully evaluated. Patients with evidence of metastatic sarcoma of the liver and patients with direct invasion of the liver from a contiguous intra-abdominal primary tumour were excluded from analysis. Eastern Cooperative Oncology Group (ECOG) performance status¹² at the time of diagnosis of primary liver sarcoma was recorded retrospectively.

Comparison and survival distributions were performed with the log rank test. Survival curves were generated using the Kaplan–Meier method.

Results

Demographic data

There were 13 men and seven women (ratio 1.9:1) with a mean age of 56 (median 59, range 23–80) years. Only one patient had a known risk factor for hepatic sarcoma with a history of thorium dioxide colloid (Thorotrast, American Cyanamid Company, Stamford, CT, USA) exposure during a carotid angiogram done 23 years before the diagnosis of a primary hepatic angiosarcoma.

Clinical presentation

Pain (ten patients), fever and chills (eight) and fatigue (six) were the most common presenting symptoms. One patient presented with hypoglycaemia. No patient had nausea, vomiting or jaundice. An abdominal mass or hepatomegaly (ten) and weight loss (eight) were the most common physical signs.

Serum alkaline phosphatase concentrations were raised in every patient and aminotransferase levels were more than twice normal in one patient. Total bilirubin was raised (3.6 mg/dl) in one patient only. The serum albumin concentration was depressed in six patients. None of the three patients with primary hepatic angiosarcoma presented with Kasabach–Merritt syndrome, as described by others¹³.

ECOG performance status was determined retrospectively. Nineteen patients were ECOG performance level 0 (normal activity) on admission. One patient was

Table 2 Primary hepatic sarcoma: distribution by histological type and grade

Histological type	No. of patients	High grade	Low grade
Leiomyosarcoma	5	5	0
Malignant solitary fibrous tumour	4	2	2
Epithelioid haemangioendothelioma	3	0	3
Angiosarcoma	3	2	1
Carcinosarcoma	2	2	0
Embryonal sarcoma	1	1	0
Fibrosarcoma	1	1	0
Pleomorphic liposarcoma	1	1	0
Total	20	14	6

symptomatic only with strenuous activity (ECOG 1). In 16 patients, the diagnosis of hepatic sarcoma was made by a preoperative liver biopsy. For the other four patients, the diagnosis of sarcoma was confirmed only after resection.

Diagnostic studies

Chest radiographs were normal in all patients. Abdominal CT was performed in 19 patients and was abnormal in 18. Multicentric tumour was noted in three patients, although seven patients had multicentricity confirmed pathologically. Neither vascular invasion nor distant metastases were noted before operation on CT. Hepatic ultrasonography was carried out in 15 patients and a tumour was apparent in 14. Ultrasonography detected multicentricity in only two of five patients studied. No hepatic angiograms were performed.

Pathology

Leiomyosarcoma ($n = 5$) was the most common histological type of sarcoma (Table 2); all were high-grade tumours. One had epithelioid features and another had intra-abdominal lymph node metastasis along the common hepatic artery. Four patients had malignant solitary tumours (two high grade; two low grade). Other histological types included three low-grade epithelioid haemangioendotheliomas (15 per cent), three angiosarcomas (two high grade, one low grade), two high-grade carcinosarcomas, one high-grade embryonal sarcoma, one high-grade fibrosarcoma and one high-grade pleomorphic liposarcoma (Table 2).

Mean tumour diameter was 14 (median 15, range 4–23) cm. The disease arose from the right liver in 13 patients, the left liver in five and was bilateral in two. Tumours were multicentric in seven patients. Resection margins were negative for tumour in 19 patients, including the liver transplantation patient. Two tumours had diaphragmatic

Table 3 Site of distant metastases from primary hepatic sarcoma

Site of distant metastases	No. of patients
Lung and pleura	4
Adrenal gland	2
Bone	1
Oesophagus	1
Duodenum	1
Brain	1
Total	10

invasion. The extent of surgical margins was reported in nine patients: mean 17 (median 10, range 2–50) mm. Two patients had invasion into the hepatic veins.

Therapy

No patient received preoperative therapy. Surgical resection was potentially curative in 19 patients; one patient had tumour at the resection margin. Intraoperative ultrasonography was performed in nine patients and diagnosed hepatic vein involvement in two patients. The most common surgical procedure was a right hepatectomy performed in 12 patients, followed by single segmentectomy in three, left hepatectomy in two, subsegmental resection in one patient and extended right hepatectomy in one patient. One patient with extensive bilobar low-grade epithelioid haemangioendothelioma had an orthotopic liver transplantation. There was one death 30 days after operation. Because of a close resection margin, radiation therapy (15 Gy of 12-MeV electrons) was delivered intraoperatively in one patient.

Six patients received chemotherapy at the time of tumour relapse (mean 9 months following surgery). Doxorubicin was used in five patients and ifosfamide and etoposide were used in one patient. Five of these six patients died from disseminated disease at a mean of 16 (range 6–25) months after the initiation of chemotherapy. The other patient, with a high-grade fibrosarcoma, died without known residual tumour. His chemotherapy consisted of doxorubicin in combination with cyclophosphamide, cisplatin and Henkel compound (Henkel, KGaA, Dusseldorf, Germany).

Pattern of recurrence

Survival free of any recurrence was 56 (95 per cent confidence interval (c.i.) 37–84) per cent at 1 year, 38 (21–70) per cent at 3 years and 28 (12–65) per cent at 5 years. Thirteen patients had tumour recurrence with a median time to recurrence of 264 days (range 35 days to 5.9 years). Multiple sites of failure (hepatic, peritoneal and distant

metastases) were present in six of the 13 patients. Distant metastases (ten patients) and intrahepatic recurrence (six patients) were the predominant sites of initial treatment failure.

Survival free of distant metastases was 65 (95 per cent c.i. 46–92) per cent at 1 year, 46 (27–78) per cent at 3 years and 34 (16–74) per cent at 5 years. Sites of distant metastasis are listed in Table 3. The median patient survival after distant recurrence was only 8.7 months. Five of these patients with distant metastases also had hepatic, peritoneal or both forms of recurrence. Six patients with distant relapse underwent additional surgical resection. These procedures included wedge resection of pulmonary metastases (two patients), excision of incisional recurrence (one patient), excision of metastases in the right perinephric fat and adrenal gland with intraoperative and postoperative radiotherapy (one patient), excision of a pleural mass (one patient), and resection of a pedunculated leiomyosarcoma in the oesophagus 3 years after hepatic resection of a primary low-grade malignant solitary fibrous sarcoma (one patient). Although all six patients had tumour-free resection margins of the metastases, only one is alive without recurrence. This patient underwent an orthotopic liver transplantation and had a solitary lung metastasis excised 6 months later. He remains alive and free of disease 5 years after resection of the pulmonary metastasis. The other five patients have died with disseminated metastatic disease (median 10 (range 2–12) months).

Six patients developed solitary intrahepatic recurrence after operation, two without other sites of recurrence. The other four patients had multiple sites of disease failure. Survival free of intrahepatic recurrence was 77 (95 per cent c.i. 60–100) per cent at 1 year, 71 (53–96) per cent at 3 years and 71 (53–96) per cent at 5 years. The median duration of survival of patients after recurrence was 8.6 months. Resection of intrahepatic recurrence was performed in only one patient. However, this patient, who had a high-grade embryonal sarcoma, died 15 months later from intrahepatic and extrahepatic tumour recurrence. The other patient who developed isolated intrahepatic recurrence died from liver failure secondary to hepatic venous outflow obstruction. One patient with incomplete resection of primary hepatic sarcoma died 21 months after operation from tumour progression.

Survival free of peritoneal metastases was 74 (95 per cent c.i. 54–100) per cent at 1 year, 74 (54–100) per cent at 3 years and 74 (54–100) per cent at 5 years. Five patients developed this type of recurrence. Median patient survival from the time of recurrence was 9 months, and all patients have died from disease progression.

The incidence of tumour recurrence was comparable for patients who had unifocal (eight of 13 recurred) or multifocal

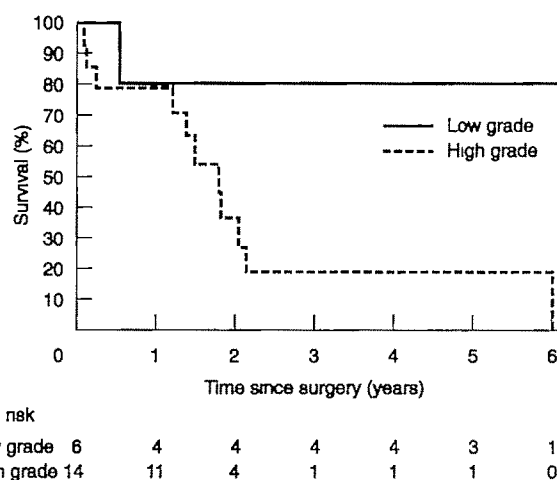


Fig. 1 Influence of tumour grade on survival after surgical resection of primary hepatic sarcoma. $P=0.03$ (log rank test)

(five of seven recurred) hepatic sarcomas ($P=0.17$). A preresection tumour biopsy did not have a measurable impact on disease recurrence. Of the 16 patients who had an incisional biopsy, ten developed disease recurrence, compared with three of the four patients who did not have a preliminary biopsy ($P=0.43$). The extent of hepatic resection had no impact on recurrence-free survival. Two of four patients who had a subsegmental or segmental hepatic resection had a recurrence compared with 11 of 16 patients who underwent more extensive operations ($P=0.44$).

Patient survival

At a median patient follow-up of 19 (mean 27, range 1–73) months, eight patients were alive, six of whom were free of disease. Three other patients had no evidence of recurrent sarcoma at the time of death (follow-up 1, 3 and 21 months after operation). Nine patients died from disseminated disease.

Overall 1-, 3- and 5-year survival estimates were 79 (95 per cent c.i. 63–100), 37 (20–69) and 37 (20–60) per cent respectively. Histological grade ($P=0.03$) was a significant determinant of overall survival (Fig. 1). Despite complete resection, patients with high-grade tumours had a 5-year survival rate of only 18 per cent (5–62) compared with 80 per cent (52–100) in patients with low-grade tumours. Patient age, sex, tumour size, multicentricity and free resection margins were not statistically significant prognostic variables for patient survival.

Discussion

Primary hepatic sarcomas are extremely rare tumours that include a heterogeneous group of histological types. The

Liver Cancer Study Group of Japan³ reported ten patients with primary liver sarcoma among 12 887 cases of primary liver cancer. Immunohistochemistry is necessary to subclassify hepatic sarcomas and differentiate sarcomas from the more common hepatic malignancies¹⁴. Extrahepatic sarcomas, especially intraperitoneal primaries, may spread to the liver. The present study excluded extrahepatic sarcomas by history, diagnostic tests and intraoperative findings.

Unlike most primary hepatocellular carcinomas, sarcomas are not associated with cirrhosis or a history of hepatitis. The aetiology of most primary sarcomas of the liver is unknown. Angiosarcomas have been associated with exposure to thorium dioxide colloid (Thorotrast), arsenic, vinyl chloride monomer and therapeutic radiation^{15–17}. One of the present patients, with a primary hepatic angiosarcoma, had previous exposure to Thorotrast. Forbes *et al.*¹⁸ and others^{19,20} also identified chronic oral contraceptive use as a possible risk factor for hepatic sarcoma. None of the patients in the present study had known exogenous oestrogen exposure. There are rare reports of hepatic sarcomas, along with other soft sarcomas, breast carcinomas, brain tumours, adrenocortical carcinomas, leukaemias, lymphomas and lung carcinomas, in members of Li-Fraumeni kindreds^{6,21,22}. There was no evidence of any patients with genetically transmitted tumours in this study.

Treatment is generally delayed in hepatic sarcomas owing to the absence of early symptoms. Lawrence *et al.*²³ reported a median delay of 4 months from the time a patient discovered an abdominal mass until the initial physician visit. Further delays in diagnosis postponed definitive therapy for another 6 months. In contrast, patients in the present study most commonly presented with right upper quadrant pain alone (ten patients) or with an abdominal mass (ten). Patients with hepatic sarcoma occasionally develop hypoglycaemia, acute abdomen from tumour rupture, congestive heart failure, ascites or oedema^{6,18,21}. Other than one patient with hypoglycaemia and fatigue, no patient in the current study presented with these uncommon findings. The authors have not found other clinical or imaging features to be pathognomic of primary hepatic sarcomas.

CT can accurately define the extent, size and anatomical relationship of the tumour. In this series, CT demonstrated the tumour mass in 18 of 19 patients. In one patient, the tumour was not visualized. Tumour vascularity is variable but, unlike hepatocellular carcinomas, these tumours do not regularly invade the portal veins. Although 16 patients had a preoperative biopsy, many biopsies were performed before referral to this centre. Pathological confirmation is not necessary before resection of a primary hepatic sarcoma. Rapid tumour recurrence on Gerota's fascia may have

resulted from needle biopsy-induced tumour spillage in one patient.

Currently surgery is the treatment of choice for patients with sarcoma and may extend survival in these patients. Hepatic resection or liver transplantation, depending on the intrahepatic extent of disease, offers the only potential chance of cure and should be the first priority in patients with primary hepatic sarcoma. Other than complete resection, no other treatment variables have any prognostic impact for patients with hepatic sarcoma.

Some studies on soft tissue sarcomas^{19,20,24} have reported that a single tumour mass results in better survival than multiple tumours. Tumour size and the presence of free resection margins also significantly affected prognosis in these reports. In the present study, however, there was no statistical difference in survival dependent on tumour size, multicentricity or clear resection margins, although these findings may be due to the small number of patients. Intraoperative radiation therapy was used in only one patient with close resection margins. While no recurrence was apparent in the treatment field, the patient died from diffuse peritoneal and distant metastases. Whenever possible, a 1-cm resection margin of normal liver tissue should be obtained. Tumour ablation by cryotherapy or radiofrequency techniques may be an appropriate alternative to resection, but no data exist to prove this assertion.

In this study, despite complete resection, patients with high-grade tumour had a 5-year survival rate of only 18 per cent compared with 80 per cent for patients with low-grade tumours that had been excised completely. These results are similar to those reported by Conlon *et al.*²⁴ for primary gastrointestinal sarcomas.

Patterns of recurrence for hepatic sarcomas are similar to those for primary sarcomas at other sites. In the authors' experience, distant metastases were the most common form of recurrence, followed by hepatic and peritoneal recurrences. Multiple sites of recurrence occurred in six of 13 patients with tumour recurrence. These observations suggest that isolated hepatic recurrence is an unlikely pattern of failure compared with diffuse metastases.

Multimodality therapy has been used routinely for extremity sarcomas, but not for primary hepatic sarcomas. Combining radiation and surgical resection has been recommended for the eradication of microscopic residual tumour when the margin of resection is limited²⁵. However, whether the combination of radiation and surgery will reduce the incidence of local failure in hepatic sarcomas remains unclear. There is also no evidence that adjuvant chemotherapy is efficacious for primary hepatic sarcomas in adults; no data show improved survival for patients so treated^{1,2,6,7,18,26–28}.

Because of a high risk of failure, especially with high-grade sarcomas, a multidisciplinary approach, including effective local and systemic therapies, needs to be developed to improve patient survival. Routine adjuvant chemotherapy cannot be recommended at present with the data available. Eight of ten patients with distant tumour recurrence in this study succumbed in less than 2 years. Follow-up after surgical resection may allow early diagnosis of limited local or distant recurrence and potentially curative salvage surgical therapy in selected patients. Resection of isolated pulmonary recurrences should be considered, since some of these patients can be salvaged.

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Endoscopic stent placement for pancreaticocutaneous fistula after surgical drainage of the pancreas

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Background: Spontaneous closure of an external pancreatic fistula is unlikely when a concomitant downstream obstruction of the pancreatic duct inhibits downstream flow. Early endoscopic retrograde pancreatography (ERP) and stent insertion may enhance fistula closure in these patients.

Methods: The results of endoscopic stenting of the pancreatic duct were evaluated in 15 patients with an external pancreatic fistula that developed after operative necrosectomy and debridement of the pancreas (seven men and eight women, median age 45 (range 25–68) years).

Results: Median drainage before ERP was 50–800 ml/day, with an amylase content of 21 000–493 000 units/l. ERP was performed after a median time of 35 days and revealed leakage of the duct and a downstream obstruction in all patients. An endoprosthesis was inserted beyond the site of obstruction. Within a median time of 10 (range 2–64) days drainage stopped in all patients. In one patient ERP failed and pancreaticojejunostomy was performed. During follow-up (median 24 (range 2–55) months) three patients required resection of the pancreatic tail because of pseudocyst formation, all of whom originally had leakage from the tail area.

Conclusion: Based on these data, an active approach for external pancreatic fistula seems warranted. Early ERP and stent insertion enhances fistula resolution, facilitates wound care and surgery is postponed or even avoided.

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Introduction

Pancreaticocutaneous fistula develops in every fourth patient as a complication after pancreatic debridement^{1–3}. It is a serious condition frequently seen in already critically ill patients with a substantial mortality rate of between 8 and 10 per cent⁴. The treatment of this complication is not well defined. With conservative treatment, including fasting, total parenteral nutrition, high-dose pancreatic enzymes or octreotide, approximately 80 per cent of external fistulas close spontaneously, although this may take up to 6 months^{1,3,5}. Spontaneous closure of postoperative pancreatic fistulas may take even longer or fail when a downstream obstruction of the pancreatic duct maintains the fistula. These patients may then be treated surgically by surgical drainage or resection¹.

Early endoscopic retrograde pancreatography (ERP) may be useful in selection of patients who are unlikely to benefit from conservative methods. In case of a downstream

duct obstruction an endoprosthesis may be inserted into the pancreatic duct, which may result in more rapid closure of the fistula and a low recurrence rate^{6,7}. In the present study the results of endoscopic stenting of the pancreatic duct were evaluated in 15 patients with a pancreaticocutaneous fistula that followed surgical debridement of (peri)pancreatic tissue.

Patients and methods

Between 1992 and 1998, 48 patients underwent debridement of (peri)pancreatic tissue. Twenty-one of these 48 patients developed a pancreaticocutaneous fistula after operation. Pancreatic fistula was defined as persistent or increasing drain production with an amylase content higher than three times the serum amylase level. In 16 patients ERP was performed, and in 15 of these 16 patients a downstream pancreatic duct obstruction was shown (seven men and eight women, median age 45 (range 25–68) years). The

other five patients did not undergo pancreatography for unknown reasons, although early ERP was not standard management in earlier days.

Results

Median drain production after drainage of the pancreas before ERP was 125 (range 50–800) ml/day with a median amylase content of 121 000 (range 21 000–493 000) units/l. Six patients had a high-output fistula (more than 200 ml/day). Before ERP, four patients were treated with octreotide, which resulted in a decrease in fistula output, but without complete resolution.

ERP was performed after a median of 35 (range 13–189) days of persistent drain production. Leakage of contrast from the pancreatic duct was confirmed in all patients, from the pancreatic head in five patients, from the corpus in four and from the tail in four patients. In two patients leakage was observed from both the corpus and the tail area. Ductal outflow was found to be inhibited owing to obstruction of the main pancreatic duct ($n = 12$), pancreas divisum with a relative outflow obstruction at the site of the minor papilla ($n = 2$) or pancreatic stones ($n = 1$) (Fig. 1a). A 7-Fr endoprosthesis of variable length (median length 10 (range 5–14) cm) was inserted into the pancreatic duct in 13 patients (Fig. 1b). The stent was positioned beyond the site of leakage in nine patients; the four remaining patients, all with leakage from the tail, received a short stent (5 or 7 cm). In two patients insertion of an endoprosthesis failed: a subsequent pancreaticojejunostomy was performed in one patient and the other patient refused further ERP.

Within a median time of 10 (range 2–64) days after stent insertion, drain production stopped in all 13 patients. In three of these 13 patients drain production decreased dramatically immediately after stent insertion, but did not stop completely until 31, 55 and 64 days later. In another patient the drain produced fluid again 5 days after stent insertion because the stent became clogged. The drain production stopped after exchange of the stent. The endoprotheses were removed routinely after 6 weeks, after a control pancreatogram showed no signs of leakage (Fig. 1c). In the patient in whom a pancreaticojejunostomy was performed, drain production stopped after 14 days. The patient who refused a second pancreatogram was discharged with the drain *in situ*, returned to her home country and was lost to follow-up.

During a median follow-up of 24 (range 2–55) months, three patients who originally suffered leakage from the pancreatic tail underwent distal pancreatectomy because of pseudocyst formation in the pancreatic tail.



Fig. 1 Endoscopic retrograde pancreatography (ERP) of a patient with an external pancreatic fistula after surgical drainage of the pancreas. **a** Free extravasation of contrast fluid from the pancreatic duct is revealed together with a pseudocyst in the corpus. **b** An endoprosthesis is inserted into the pancreatic duct. **c** After 6 weeks the endoprosthesis is removed and control ERP shows no signs of leakage from the pancreatic duct

Discussion

Although conservative treatment of external pancreatic fistulas leads to resolution in the majority of cases, the prolonged hospitalization causes discomfort for the patient and is costly. Failure of conservative treatment is often associated with the presence of a downstream obstruction of the pancreatic duct^{1,7} and for many years surgical drainage or resection was the next logical therapeutic step^{1-3,8}. More recently, insertion of an endoprosthesis into the pancreatic duct was shown to be a way of lowering intraductal pressure in these patients and enhancing closure of the fistula^{6,7}. In the present series this method was safe and highly effective in all patients. In ten of 13 patients, the fistula, regardless of the output, resolved within days and drains could be removed. In three patients drain production decreased dramatically although drains could not be removed until weeks later.

To enhance fistula closure, exocrine pancreatic secretion may be lowered by the administration of octreotide or its analogue. This has been a focus of recent studies. In one retrospective study of 45 patients, fistulas resolved in a shorter period (within 12 days) in the eight patients treated with octreotide combined with total parenteral nutrition (TPN) than in the 37 patients treated with TPN and glucagon or calcitonin⁹. In another study of eight patients with high-output external fistulas, administration of somatostatin resulted in closure of the fistula in seven patients within 23 days¹⁰.

The efficacy of octreotide in patients with a downstream pancreatic duct obstruction is unknown. In this series only four patients were treated with octreotide in the early years of the study. In these patients the fistula output did diminish but did not stop. Therefore, octreotide was no longer administered routinely in such patients.

Persistent fistulas can be treated efficiently by surgery. The success rate of fistula closure after different surgical procedures was 83 per cent in a series of 24 patients, but was associated with a mortality rate of 8 per cent and morbidity rate of 13 per cent⁸. In another small series surgical drainage of the pancreatic duct was effective in all six patients with no death and no recurrence during 6–48 months of follow-up¹¹. Patients with the so-called 'isolated remnant syndrome' may be more amenable to surgical treatment. When the pancreatic tail is relatively intact, but ductally isolated owing to massive necrosis of the head and corpus, endoscopic drainage is not suitable. These patients should probably be treated conservatively and, in the case of a persistent fistula, may undergo resection of the pancreatic tail.

Endoscopic stent placement into the pancreatic duct was highly successful in a series of five patients with an internal

or external pancreatic fistula. The fistulas resolved quickly and no leakage recurred during a follow-up of 14–30 months⁷. The inserted stent possibly bridges the leak in the pancreatic duct and thus acts as a mechanical seal. Alternatively the stent forms the route of the least resistance for the flow of pancreatic secretions towards the duodenum. In the latter case a short stent, i.e. one that does not necessarily bridge the leak but only bypasses the pancreatic sphincter, would suffice. In that way possible stent-induced damage to the pancreatic duct is avoided. In the majority of patients in this series the endoprosthesis was positioned beyond the site of leakage. However, pseudocyst development necessitated surgery during follow-up in three of six patients with leakage from the pancreatic tail.

The possibility that the fistulas in the present series would have closed spontaneously after prolonged conservative treatment cannot be excluded. However, a more active approach in patients with a well established external fistula (i.e. without active necrotizing pancreatitis with pus or debris) seems beneficial. Based on the present study and the literature it would seem advisable to perform ERP early after treatment with octreotide for 7 days without reduction of drain production or after 14 days when residual production persists despite initial reduction. Subsequent insertion of a short endoprosthesis into the pancreatic duct is indicated especially when downstream duct obstruction is observed at ERP. Using this approach recovery time is shorter, wound care is facilitated and surgery may be performed later as an elective procedure or may even be avoided.

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Effects of hepatic blood inflow occlusion on liver regeneration following partial hepatectomy in an experimental model of cirrhosis

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Background: Hepatic blood inflow occlusion during hepatectomy may influence postoperative liver regeneration. The aim of this study was to investigate the influence of hepatic blood inflow occlusion on liver regeneration following partial hepatectomy in thioacetamide-induced cirrhotic rats.

Methods: Forty-three cirrhotic Wistar-Furth rats were randomly assigned to three groups. Rats in group 1 underwent 64 per cent hepatectomy alone, those in group 2 were subjected to 15 min hepatic blood inflow occlusion followed by 64 per cent hepatectomy, and animals in group 3 were subjected to 30 min inflow occlusion followed by 64 per cent hepatectomy. Liver function, 5-bromo-2'-deoxyuridine (BrdU) labelling index and percentage of initial liver weight on days 1, 2 and 7 posthepatectomy were assessed.

Results: Rats in groups 1 and 2 had a significantly higher serum albumin level and a markedly lower alanine aminotransferase level than animals in group 3 on day 1 posthepatectomy ($P < 0.05$). There was no significant difference in the serum level of total bilirubin of the three groups on days 1, 2 and 7. The BrdU labelling index was significantly higher in groups 1 and 2 than in group 3 animals on day 1 posthepatectomy ($P < 0.01$ and $P < 0.05$ respectively). Percentages of initial liver weight were similar in groups 1, 2 and 3 on days 1, 2 and 7 after hepatectomy.

Conclusion: Hepatic blood inflow occlusion for up to 30 min suppressed DNA synthesis and hepatocyte proliferation at an early posthepatectomy stage and consequently delayed recovery of liver function in cirrhotic rats. However, it did not affect restoration of liver mass or survival after 64 per cent hepatectomy.

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Introduction

Complete surgical excision of tumour offers the best hope of long-term survival or cure for patients with hepatocellular carcinoma^{1–3}. Intraoperative bleeding is commonly encountered in patients with underlying liver cirrhosis. As excessive intraoperative blood loss predisposes to the development of postoperative morbidity and mortality^{4,5}, and blood transfusion shortens the duration of recurrence-free survival^{6–8}, a number of vascular occlusion techniques have been used in an attempt to reduce blood loss during liver resection. The technique of hepatic blood inflow occlusion (Pringle's manoeuvre) is commonly employed during major liver resection^{9–13}.

Many authors believe that human liver, even a cirrhotic liver, can well tolerate inflow occlusion and warm ischaemia

for up to 30–60 min at normal body temperature^{14–16}. Whether prolonged inflow occlusion has any influence on liver regeneration following hepatectomy is not well documented. The present study was designed to investigate the effects of hepatic blood inflow occlusion on liver regeneration after non-fatal hepatectomy using an established cirrhotic rat model.

Materials and methods

Animals

Eight-week-old male Wistar-Furth rats with mean (s.d.) body-weight of 281 (29) g, obtained from the Animal Centre at the Chinese University of Hong Kong, were used. The rats were housed in wire cages in a room with controlled

temperature (21°C) and a 12-h alternating light–dark cycle, and offered free access to drinking water and rat chow throughout the experiment.

Induction of liver cirrhosis

Liver cirrhosis was induced by intraperitoneal injection of a 4 per cent aqueous solution of thioacetamide (Sigma, St Louis, Missouri, USA) at a dose of 20 mg per 100 g body-weight three times a week for eight consecutive weeks¹⁷.

Randomization and operation

One week after completion of thioacetamide treatment, rats underwent laparotomy through an upper midline incision under inhalation anaesthesia with 2 per cent halothane (Zeneca, Macclesfield, UK) mixed with oxygen. All hepatectomies were carried out in the morning to minimize the diurnal effects on liver regeneration. Rats whose livers showed macroscopic nodules of various sizes and sclerosis were selected for the study and randomly assigned to group 1 ($n = 13$), 2 ($n = 15$) or 3 ($n = 15$). In group 1, excision of left lateral and median lobes of the liver was performed alone. In group 2, the rats underwent 15 min inflow occlusion followed by excision of left lateral and median lobes of the liver. In group 3, the rats underwent 30 min inflow occlusion preceding excision of left lateral and median lobes of the liver. Inflow occlusion was performed by clamping the hepatic pedicle at the hilum with a vascular clip. The abdominal incision was closed after hepatectomy. The resected livers were weighed and saved for subsequent histological examination. To determine the percentage of liver resected, six further rats were killed immediately after partial hepatectomy and the remnant liver was excised and weighed. The mean(s.d.) percentage of the resected livers was 63.6(3.4) per cent.

After operation the rats were offered free access to drinking water and chow; no other special treatments were given. On days 1, 2 and 7 posthepatectomy, four to six rats in each group were killed. One hour before death, a dose of 50 mg per kg body-weight of 5-bromo-2'-deoxyuridine (BrdU) (Boehringer Mannheim, Mannheim, Germany) was injected intraperitoneally¹⁸. At the time of killing, the rats were anaesthetized, blood samples were drawn from inferior vena cava for subsequent analysis of liver function, and the remnant liver was excised and weighed. The excised liver was fixed in 4 per cent buffered formaldehyde and subjected to a standard procedure for paraffin embedding.

Assessment of liver regeneration

To evaluate the proliferation of hepatocytes in the remnant liver, the BrdU labelling index, an index for DNA synthesis

in hepatocytes, was used^{18–20}. Incorporation of BrdU in hepatocytes was assessed immunohistochemically in formalin-fixed paraffin-embedded liver tissues by the avidin–biotin complex method^{18,19}. Liver tissue sections 4 µm thick were cut and mounted on slides coated with 0.2 per cent gelatin solution (Sigma). After deparaffinization and hydration, the sections were incubated with 3 per cent hydrogen peroxide for 5 min to eliminate endogenous peroxidase activity. Non-specific protein binding was blocked by treating the sections with 1.5 per cent normal horse serum (Vector Laboratories, Burlingame, California, USA) for 20 min. The sections were then incubated with anti-BrdU monoclonal antibody (Calbiochem, San Diego, California, USA) diluted 1 : 125 for 1 h at room temperature. Binding of primary antibody at antigenic sites was detected by successive incubation with antimouse biotinylated immunoglobulin G (diluted 1 : 100) and avidin–biotin–peroxidase complex (diluted 1 : 100; Vector Laboratories) for 30 min respectively, and diaminobenzidine for 10 min. Finally the sections were lightly counterstained in Gill's haematoxylin, dehydrated and mounted. Positively stained nuclei in hepatocytes appear brown under light microscopy. By randomly counting at least 1000 hepatocytes at a magnification of $\times 400$, the number of BrdU-labelled nuclei per 1000 hepatocytes was designated as the BrdU labelling index.

Hepatic regeneration rate

The percentage of initial liver weight, calculated with the following equation, was used to reflect the hepatic regeneration rate²¹:

$$\text{Percentage of initial liver weight} = A/E \times 100$$

where A represents the actual remnant liver weight with respect to body-weight at the time of death, and E represents the whole liver weight with respect to body-weight before hepatectomy. E was estimated by $R/0.636$, where R represents weight of the resected liver at the time of hepatectomy.

Statistical analysis

Results are expressed as mean(s.d.). The SPSS software package version 9.0 (SPSS, Chicago, Illinois, USA) was used for statistical analysis. Analysis of variance was employed to compare differences between groups. $P < 0.05$ was considered statistically significant.

Results

Histological examination confirmed the presence of micro-nodular cirrhosis (Fig. 1). One rat in group 2 and another in

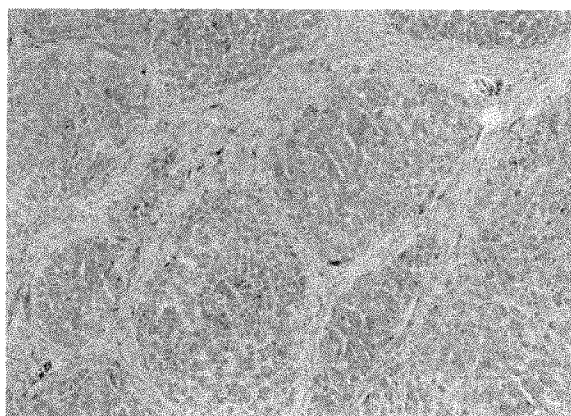


Fig. 1 Light microscopic features of thioacetamide-induced cirrhosis (haematoxylin and eosin staining; original magnification $\times 63$)

Table 1 Preoperative body-weight in the three groups

	Mean(s.d.) preoperative body-weight (g)		
	Group 1	Group 2	Group 3
Day 1	386(38) (n=5)	374(37) (n=6)	394(13) (n=4)
Day 2	365(33) (n=4)	410(54) (n=4)	386(26) (n=6)
Day 7	337(27) (n=4)	364(31) (n=4)	374(27) (n=4)

There were no significant differences between the groups

group 3 died after operation. All other rats survived until killed. There was no significant difference in preoperative body-weights between animals in the three groups (Table 1).

Liver function tests

Serum albumin levels of rats in groups 1 and 2 were significantly higher than those in group 3 on day 1 after hepatectomy (10.6(1.0) g/l in group 1 and 10.3(1.0) g/l in group 2 *versus* 8.9(0.7) g/l in group 3; both $P < 0.05$), and serum albumin concentration in group 1 remained significantly higher than that in group 3 on day 2 (9.7(1.0) *versus* 8.3(0.7) g/l; $P < 0.05$). There were no significant differences between groups on day 7 (Fig. 2). Serum alanine aminotransferase concentration in groups 1 and 2 was significantly lower than that in group 3 on day 1 posthepatectomy (both $P < 0.05$). There were no significant differences between the groups on days 2 and 7 (Fig. 3). Serum total bilirubin level was lower in rats in groups 1 and 2 than in animals in group 3 on days 1 and 2, but the difference was not statistically significant. On day 7 there was no remarkable difference between the groups (Fig. 4).

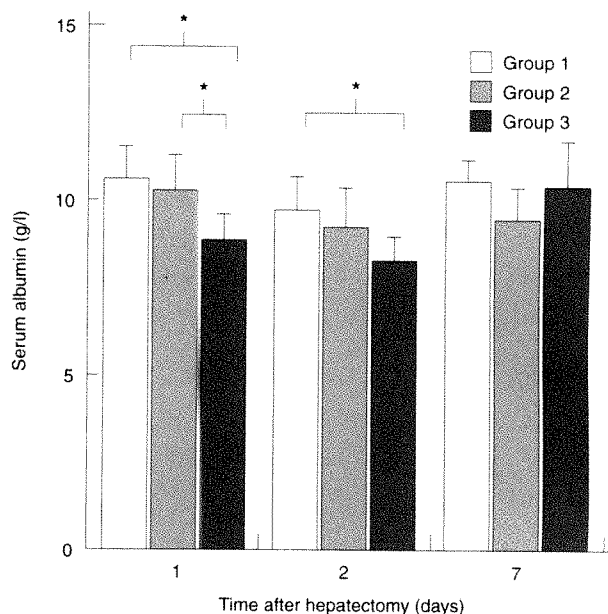


Fig. 2 Serum albumin concentration in the three groups at days 1, 2 and 7 posthepatectomy. Values are mean(s.d.). * $P < 0.05$ (analysis of variance)

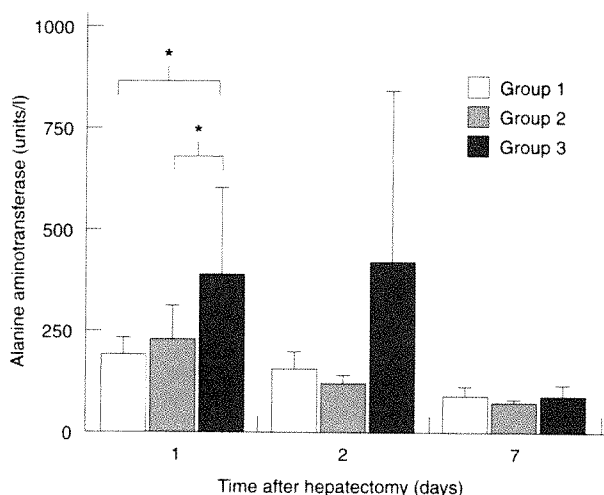


Fig. 3 Alanine aminotransferase levels in the three groups at days 1, 2 and 7 posthepatectomy. Values are mean(s.d.). * $P < 0.05$ (analysis of variance)

5-Bromo-2'-deoxyuridine labelling index

Immunohistochemical staining for BrdU in regenerating liver is shown in Fig. 5. The BrdU labelling index was significantly higher in rats in groups 1 and 2 compared with that in group 3 on day 1 after hepatectomy (81.8(31.6) and 64.3(28.7) *versus* 17.2(21.1); $P < 0.01$ and $P < 0.05$ respec-

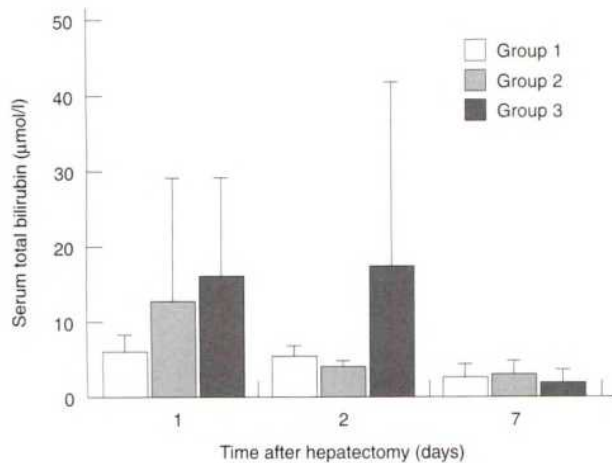


Fig. 4 Serum total bilirubin levels in the three groups at days 1, 2 and 7 posthepatectomy. Values are mean(s.d.)

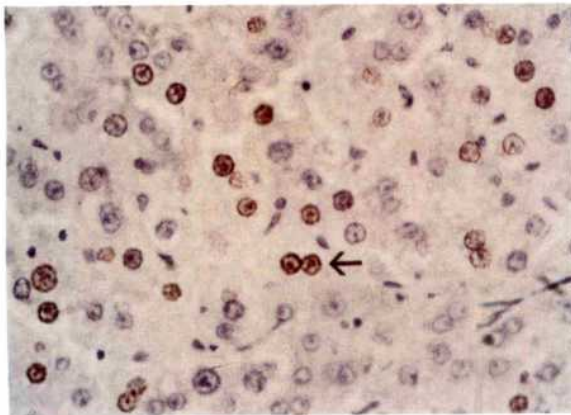


Fig. 5 Immunohistochemical staining for 5-bromo-2'-deoxyuridine in the regenerating liver. Nuclei with deposition of brownish pigment (arrow) were considered to be labelled (original magnification $\times 400$)

tively). The index remained higher in rats in groups 1 and 2 than in group 3 animals on days 2 and 7, although the difference was not significant. There were no significant differences between rats in groups 1 and 2 on days 1, 2 and 7 posthepatectomy (Fig. 6). The BrdU labelling index reached a peak on day 1 posthepatectomy and then declined on days 2 and 7 in groups 1 and 2, whereas changes were suppressed in group 3 (Fig. 6).

Hepatic regeneration rate

Hepatic regeneration, as measured by percentage of initial liver weight, was similar in rats in groups 1, 2 and 3 on days 1, 2 and 7 after hepatectomy (Fig. 7).

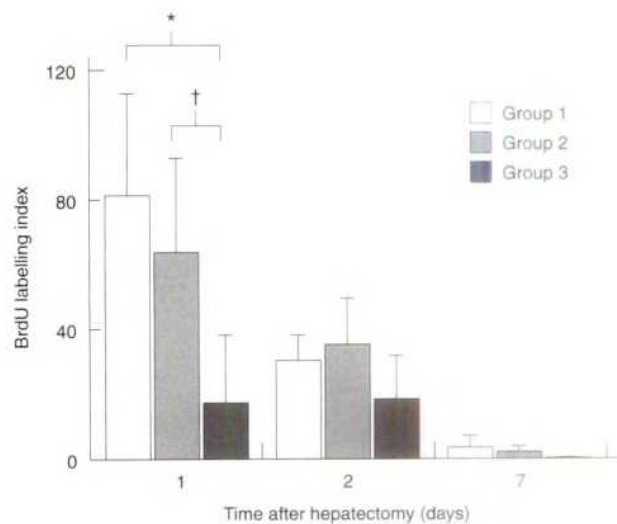


Fig. 6 5-Bromo-2'-deoxyuridine (BrdU) labelling index in the three groups at days 1, 2 and 7 posthepatectomy. Values are mean(s.d.). * $P < 0.01$, † $P < 0.05$ (analysis of variance)

Discussion

Hepatic blood inflow occlusion has been widely used in liver resection⁹⁻¹⁶ since it was first described by Hogarth Pringle in 1908. Although the Pringle manoeuvre can markedly reduce intraoperative blood loss during liver resection^{13,22}, it may induce ischaemia-reperfusion injury to the liver, particularly when vascular occlusion is prolonged. Furthermore, parenchymal transection, in the presence of cirrhosis, usually takes longer to complete, and may be responsible for the potentially hazardous hepatic injury. It has been demonstrated that temporary hepatic ischaemia induced by inflow occlusion results in the overproduction of inflammatory cytokines, including tumour necrosis factor, interleukin 6 and interleukin 8, in animal models^{23,24} and humans²⁵. These cytokines may mediate microvascular damage. Recently, Matsutomo *et al.*¹⁷ reported that continuous hepatic blood inflow occlusion for up to 60 min led to significant depletion of adenosine 5'-triphosphate in the liver and a subsequent increase in mortality rate in cirrhotic rats.

Apart from the pathophysiological events associated with hepatic blood inflow occlusion, it remains unclear whether temporary hepatic ischaemia has an influence on liver regeneration after hepatectomy, especially in the presence of cirrhosis. Mackenzie *et al.*²⁶ performed inflow occlusion of various duration followed by 70 per cent partial hepatectomy on healthy dogs, and found that temporary liver ischaemia for up to 60 min did not affect postoperative liver function or restoration of liver mass. However, pilot

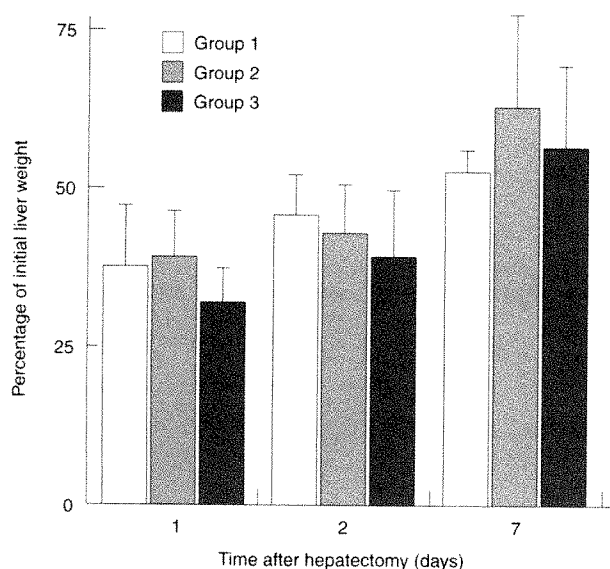


Fig. 7 Percentage of initial liver weight in the three groups at days 1, 2 and 7 posthepatectomy. Values are mean(s.d.)

studies in the present authors' laboratory have shown that extended inflow occlusion for up to 60 min resulted in a mortality rate of almost 100 per cent after 64 per cent hepatectomy. These findings led to a reduction in the inflow occlusion time to 30 min in the present study to allow assessment of hepatic regeneration and measurement of BrdU indices.

In the present study the BrdU labelling index, a popular DNA synthesis marker^{18–20}, was used to assess liver regeneration posthepatectomy, in addition to the determination of restoration of liver mass. The results showed that the BrdU labelling index on day 1 posthepatectomy was markedly lower in cirrhotic rats that had undergone 30 min inflow occlusion compared with those that had no or only 15 min occlusion, although there were no significant differences between the groups on days 2 and 7. These findings suggest that prolonged hepatic blood inflow occlusion may suppress and delay peak DNA synthesis and thus the proliferation of hepatocytes in cirrhotic liver during the early posthepatectomy phase, even though it produces little change in the overall restoration of liver mass, given the time to regenerate and that the remaining liver did not fail in the early posthepatectomy period.

Cirrhotic rats that had 30 min inflow occlusion before hepatectomy had worse liver function in terms of serum albumin and alanine aminotransferase levels on postoperative day 1 in comparison with cirrhotic rats with 15 min or no inflow occlusion. The impaired recovery of liver function in rats with prolonged inflow occlusion

during the early postoperative course may be related to suppressed proliferation of hepatocytes or ischaemic hepatocyte damage. Hence, prolonged inflow occlusion in cirrhotic liver may increase early postoperative complications, particularly hepatic dysfunction or failure, at least in part, via inhibition of early liver regeneration. This phenomenon closely resembles findings in the clinical setting, in which cirrhotic patients require a much longer time for recovery after hepatectomy.

It can be concluded from this study that prolonged inflow occlusion for up to 30 min may suppress DNA synthesis and thus proliferation of hepatocytes during the early post-hepatectomy phase in a cirrhotic rat model. However, if the ischaemia–reperfusion damage is not fatal and liver function can be maintained a delayed hepatic regeneration can occur. Thus temporary liver function support may be potentially helpful in patients with posthepatectomy liver failure.

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Compliance properties of conduits used in vascular reconstruction

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Background: Compliance mismatch between native artery and prosthetic graft used for infrainguinal bypass is implicated in the aetiology of graft failure. The aim was to quantify the elastic properties of a new compliant poly(carbonate)polyurethane (CPU) vascular graft, and to compare the compliance properties of grafts made from CPU, expanded polytetrafluoroethylene (ePTFE), Dacron and human saphenous vein with that of human muscular artery.

Methods: A pulsatile flow phantom was used to perfuse vessel and prosthetic graft segments at physiological pulse pressure and flow. Intraluminal pressure was measured using a Millar Mikro-tip catheter transducer and vessel wall motion was determined with duplex ultrasonography using an echo-locked wall-tracking system. Diametrical compliance and a stiffness index were then calculated for each type of conduit over mean pressures ranging from 30 to 100 mmHg by 10-mmHg increments.

Results: The compliance values of CPU and artery (mean over the pressure range) were similar (mean(s.d.) 8.1(0.4) and 8.0(5.9) per cent per mmHg $\times 10^{-2}$ respectively), although the elastic behaviour of artery was anisotropic unlike CPU, which was isotropic. Dacron and ePTFE grafts had lower compliance values (1.8(1.2) and 1.2(0.3) per cent per mmHg $\times 10^{-2}$ respectively, averaged over the pressure range). In both these cases, compliance and stiffness differed significantly from that of artery over a mean pressure range of 30–90 mmHg. Human saphenous vein exhibited anisotropic behaviour and, although compliant at low pressure (30 mmHg), was markedly incompressible at higher pressures.

Conclusion: Compliant polyurethane grafts offer a greater degree of compliance match than either ePTFE or Dacron.

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Introduction

When used for infrapopliteal arterial reconstruction, vascular grafts made from either expanded polytetrafluoroethylene (ePTFE) or Dacron (polyethylene terephthalate; Du Pont, Stevenage, UK) have primary patency rates of 20–30 per cent at 4–5 years^{1,2}. Mismatch in the elastic or compliance properties of prosthetic graft and adjacent native artery have been implicated^{3–5} in the aetiology of distal anastomotic myointimal hyperplasia, a major cause of prosthetic graft failure⁶. Consequently, the development of compliant alternatives to currently available prostheses has been advocated in order to improve the performance and patency rates of prosthetic bypass⁵. A new vascular graft

with a novel honeycomb microstructure made from compliant poly(carbonate)polyurethane (CPU) has been developed using an entirely new type of chemistry and stress-free manufacturing process^{5,7} which has been shown to have favourable bioresistance qualities.

Preliminary measurements have suggested that it can potentially provide a greater degree of graft–artery compliance match than either ePTFE or Dacron prostheses⁸. The aim of this study was to investigate, over a range of mean pressures, the *in vitro* dynamic compliance and stiffness properties of this new CPU prosthesis and to compare these properties with those of human muscular artery and other vascular conduits commonly used for leg bypass surgery.

Materials and methods

Vascular graft

In collaboration with industry the authors have recently developed and manufactured an improved polyurethane material from methylene di-isocyanate; polycarbonate diol and ethylene diamine in dimethylacetamide (DMAC) (2:1:0.97) containing hydrolytically/oxidatively stable aliphatic polycarbonate polyols with high hydrolase resistance, called CPU (*Fig. 1*). Its compliance has been chosen

to match that of an artery. Grafts are fabricated from a patented method involving low-temperature cast coagulation in which chemicals are added sequentially on to the surface of a rotating and transversing steel mandrel. Fillers prevent collapse of the graft structure as the solvent disperses, during phased coagulation. The filler dissolves into the coagulant so that a final single-layer structure is produced comprising an inner and outer skin and a spongy middle that permits transmission of pulsatile flow. This graft has undergone numerous *in vitro* and *in vivo* studies, including tests of biodegradation in which the graft stayed

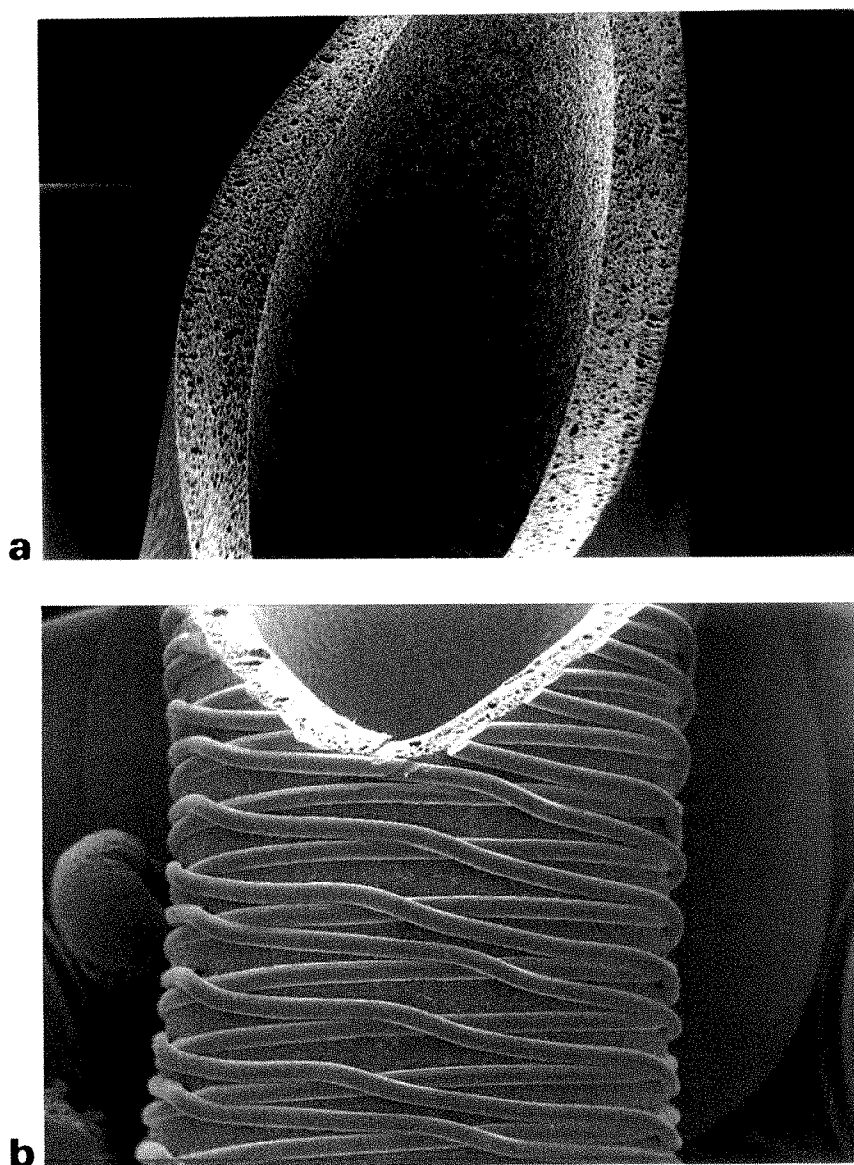


Fig. 1 Electron microscopy of compliant poly(carbonate)polyurethane grafts. **a** Non-reinforced (original magnification $\times 12.4$) and **b** externally reinforced (original magnification $\times 12.0$)

patent over 36 months in a dog aorta model. The graft has been Committee European (CE) marked, is being used worldwide as a peripheral arteriovenous fistula graft⁹ and is undergoing a randomized multicentre European clinical trial.

Flow circuit

A flow circuit specifically designed accurately to reproduce the haemodynamic characteristics of pulsatile arterial blood flow was fabricated (*Fig. 2*)¹⁰. This was then used to perfuse segments of the vascular grafts and human vessels under study. The flow model comprised a variable-speed electromagnetic centrifugal pump (Bio Medicus, Minnetonka, MN, USA), flexible plastic tubing and a fluid reservoir. A previously developed governable flow waveform conditioner was sited in series with the circuit and used to generate arterial flow waveforms. Instantaneous flow rate was measured using a 6-mm tubular flow probe connected to a Transonic Medical flowmeter system (HT207; Transonic Medical System, Ithaca, NY, USA). Serial intraluminal pressure measurements were made at discrete sites along the graft using a Millar Mikro-tip catheter transducer (Millar Instruments, Houston, Texas, USA) introduced via a Y-connection port. The perfusion solution was made using a mixture of 8 per cent low molecular weight Dextran (molecular weight 77 000 Da; Sigma-Aldrich,

Poole, UK) added to a solution of M199 (minimum essential medium), 20 per cent fetal bovine serum, 7.5 per cent sodium bicarbonate (Sigma-Aldrich), 200 mmol L-glutamine (Gibco BRL; Life Technologies, Paisley, UK), penicillin 10 000 units/ml and streptomycin 10 mg/ml, buffered at $\text{pH } 7.20 \pm 0.01$. The viscosity of this medium has previously been determined to approach that of whole human blood using a cone plate viscometer (Low-Shear 30; Contraves, Zürich, Switzerland)⁸. A gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide was bubbled through the fluid reservoir and the perfusate was maintained at 37°C via a heat exchanger (Portex, Hythe, UK). Pressure was varied by increasing the level of the fluid reservoir above the graft segment and by varying the diameter of an outflow resistance sited distally to the grafts.

Ten-centimetre test segments of CPU (5 mm internal diameter (ID); CardioTech International, Wrexham, UK), ePTFE grafts (5 mm ID; Impra, Crawley, UK), uncrimped knitted Dacron grafts (5 mm ID; Sulzer Vascutek, Inchinnan, UK) and human external iliac artery segments retrieved from organ donors were studied. Segments of macroscopically normal proximal human saphenous vein salvaged from patients undergoing Trendelenberg's procedure were also investigated. All human vessels were obtained in accordance with local ethics committee standing orders regarding experimental use of discarded human tissues, stored in Ringer's lactate solution at 4°C and studied

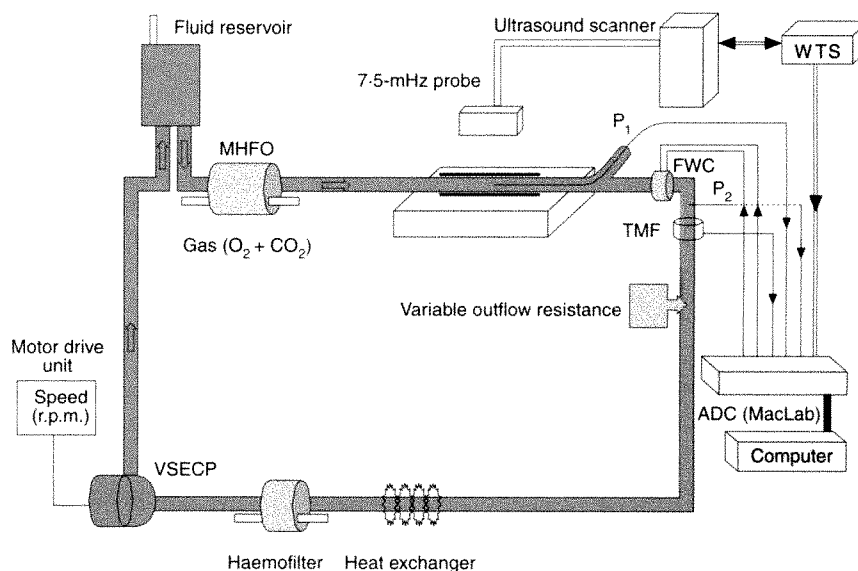


Fig. 2 Diagrammatic representation of the flow model. ADC, analogue-to-digital data acquisition recording system; FWC, flow waveform conditioner; MHFO, Maxima hollow fibre oxygenator (Medtronic, Anaheim, CA, USA); P₁ and P₂, Millar Mikro-tip catheter pressure transducer; TMF, Transonic Medical flowmeter system; VSECP, variable-speed electromagnetic centrifugal pump; WTS, wall-tracking system

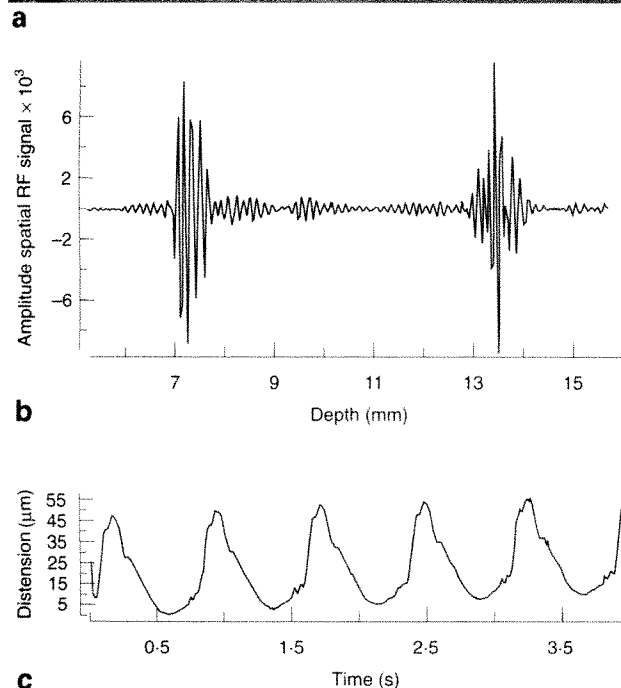
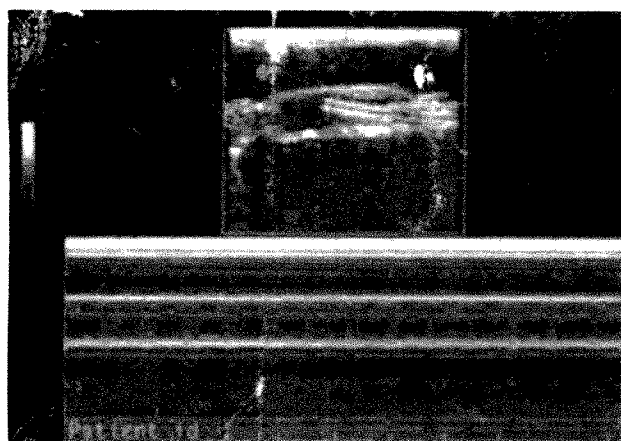


Fig. 3 **a** B- and M-mode images of saphenous vein mounted within the flow circuit. Note intraluminal pressure catheter. **b** resultant radiofrequency (RF) signal generated by anterior and posterior walls of imaged vein. **c** Distension–time curve generated by wall-tracking system

within 24 h of harvest. All prosthetic grafts were washed and degassed with 70 per cent ethanol and, to ensure minimal transmural leakage of perfusate and loss of intraluminal pressure, grafts were subjected to a preclotting procedure. This was carried out by forcing 10 ml freshly obtained whole human blood through graft interstices; once the blood had clotted, a further 10 ml fresh blood was perfused through the graft and the process repeated until no further transmural leakage of blood was observed. Grafts were then

washed in normal saline. Prosthetic graft and vessel segments were mounted in series with the flow circuit, exposed to flow and placed in a bath containing normal saline maintained at 37°C. Segments were subject to longitudinal stretch in order to reproduce the likely *in vivo* conformation¹¹. Human artery and vein were stretched by 30 per cent, and CPU and Dacron by 10 per cent; the inelastic nature of ePTFE prevented its longitudinal expansion beyond 10 per cent. All outputs were fed into a commercial analogue-to-digital data acquisition recording system (ADC/MacLab; AD Instruments, Hastings, UK).

Measurement of vessel wall movement

The change in vessel wall diameter with respect to each cardiac cycle was measured at discrete sites along the graft, with measurements taken in the sagittal plane at 90° to the long axis of the graft. Segments of the graft were scanned with a specially adapted, duplex colour-flow ultrasonography system (Pie 350; Pie Medical Systems, Maastricht, The Netherlands), with signal output to a high-resolution, echo-locked wall-tracking system (Wall Track; Pie Medical Systems). This system allowed the measurement of vessel wall movement over time by automatically tracking assigned points of the induced radiofrequency signal deemed to be representative of the anterior and posterior arterial wall. A detailed description of the system has been published elsewhere^{12,13}. Briefly, a 7.5-MHz linear array probe was immersed in the bath and positioned directly over the segment under investigation. The M-mode cursor was positioned at the midpoint of each test segment and perpendicular to the direction of flow (Fig. 3); the change in induced radiofrequency signal received from the vessel walls was then sampled over a 4-s interval. These data were then transferred to a personal computer for real-time display of the displacement waveforms of the anterior and posterior artery walls. In this way, end-diastolic and end-systolic intraluminal diameters were determined automatically over the pulsatile cycle. Measurements were made using a constant pulse pressure over a range of mean pressures (Table 1). For each mean pressure and test segment, three measurements of wall movement were made, and the experiment was repeated six times.

Data analysis and statistical methods

Diametrical compliance (C), defined as the inverse of Petersen's elastic modulus E_p ^{14,15} and expressed as per cent per millimetre of mercury $\times 10^{-2}$, was determined for each test segment at each mean pressure as follows:

$$C = (D_s - D_d/D_d) \times 10^4 / (P_s - P_d)$$

where D_s and D_d are systolic and diastolic diameter, and P_s and P_d are systolic and diastolic pressure, respectively.

Arterial wall stiffness index β , as formulated by Kawasaki *et al.*¹⁶, was calculated using

$$\beta = [\log_e (P_s/P_d)] \times D_d / (D_s - D_d).$$

For each mean pressure, the compliance and stiffness values of saphenous vein, CPU, ePTFE and Dacron were compared with those of artery using one-way analysis of variance and the Bonferroni test¹⁷.

Results

A summary of the diameter, compliance and stiffness index values for prostheses and vessel segments is provided in Table 2. Fig. 4 depicts the variation of compliance and stiffness index with respect to incrementally increased mean pressure for prostheses and vessel segments. Arterial and venous compliance was observed to behave non-linearly in response to an increase in mean perfusion pressure.

Analysis of variance revealed highly significant variance in compliance and stiffness exhibited by ePTFE, Dacron,

CPU, vein and artery ($P < 0.001$ for each mean pressure studied, from 30 to 100 mmHg). Table 3 summarizes the outcome of subsequent Bonferroni post-testing that compared, for each mean pressure, the compliance and stiffness index values of saphenous vein, CPU, Dacron and ePTFE grafts with those of artery. There were no significant differences between the compliance values of CPU and artery at mean pressures 30–60 mmHg, or between the stiffness index results at mean pressures 30–90 mmHg. Comparing Dacron and ePTFE with artery, significantly greater stiffness and lower compliance was observed at mean pressures of 30–90 mmHg and 30–100 mmHg respectively, although Dacron grafts did not differ significantly from artery in either compliance or stiffness at a mean pressure of 100 mmHg. Comparison of the elastic properties of saphenous vein to artery revealed no significant differences between the two vessel types at 30 and 100 mmHg in terms of either compliance or stiffness, although there were clearly significant disparities in compliance from 40 to 90 mmHg and in stiffness at 50, 60 and 80 mmHg.

Discussion

Arteries do not merely convey blood from one part of the circulation to another. Their elastic structure allows energy-efficient transmission of pulsatile blood flow, the simultaneous damping of excessive pressure fluctuations and the matching of the impedance characteristics of the proximal arterial tree to distal branches^{11,18}. Commercially available prosthetic vascular grafts do not reproduce these favourable characteristics. Indeed, implantation of an incompressible graft into the lower-limb arterial tree – analogous to the introduction of an impedance into an

Table 1 Flow circuit haemodynamic values

Physical parameter	Variable
Mean pressure (mmHg)*	30–100
Pulse pressure (mmHg)	60.5(0.8)
Frequency of pulsatile cycle (Hz)	1
Mean flow rate (ml/min)	132(24)
Perfusate temperature (°C)	37(1)
Perfusate viscosity (poise)	0.035(0.001)

Values are mean(s.d.). *Increased by increments of 10 mmHg

Table 2 Systolic diameter, compliance and stiffness value averaged over the entire mean pressure range, and observed at 30 and 100 mmHg

	Artery	Vein	CPU	Dacron	ePTFE
Diameter (mm)					
Averaged	6.8(0.3)	4.9(0.2)	6.1(0.8)	5.4(0.2)	5.4(0.1)
30 mmHg	6.3(1.2)	4.8(1.5)	5.9(0.2)	5.5(0.3)	5.3(0.1)
100 mmHg	7.1(1.1)	5.1(1.8)	6.9(0.4)	5.6(0.1)	5.4(0.2)
Compliance (per cent per mmHg $\times 10^{-3}$)					
Averaged	8.0(5.9)	5.0(6.7)	8.1(0.4)	1.8(1.2)	1.2(0.3)
30 mmHg	19.3(11.9)	21.0(11.0)	8.0(0.4)	1.9(0.7)	1.8(0.2)
100 mmHg	2.6(0.8)	1.5(0.4)	8.1(0.7)	1.9(1.2)	0.9(0.1)
Stiffness value (β)					
Averaged	29.9(9.0)	63.7(18.6)	20.0(8.0)	103.1(43.1)	139.0(24.8)
30 mmHg	17.8(7.3)	22.0(18.0)	35.6(2.2)	173.2(102.4)	154.0(16.4)
100 mmHg	41.8(20.0)	67.9(16.7)	11.9(1.0)	67.8(32.3)	109.0(5.2)

Values are mean(s.d.). CPU, compliant poly(carbonate)polyurethane; ePTFE, expanded polytetrafluoroethylene

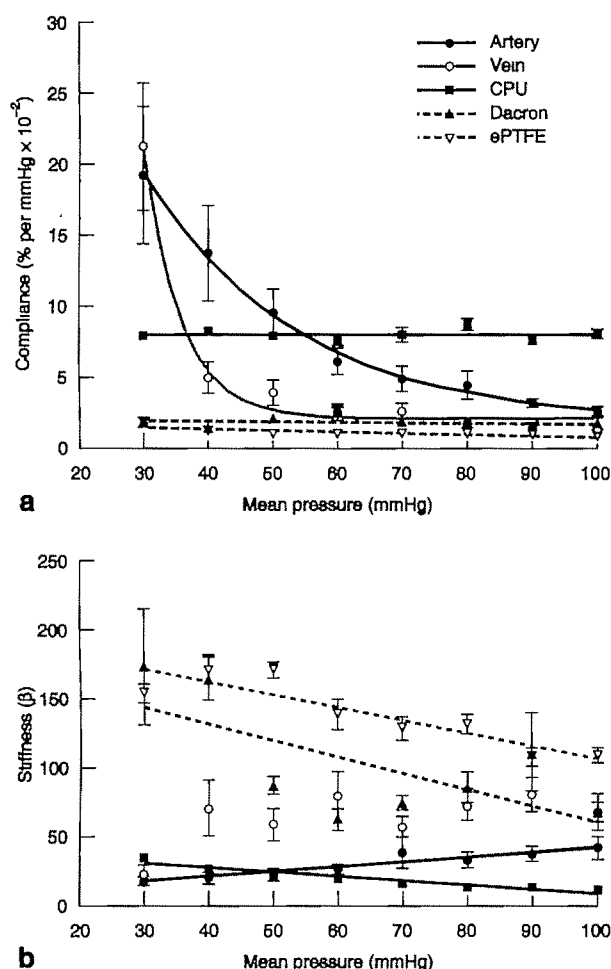


Fig. 4 **a** Compliance–mean pressure curves for vessels and grafts. Curves for anisotropic vessels (artery, vein) were generated using non-linear regression (single-phase exponential decay fit); curves for isotropic prostheses were generated using linear regression. **b** Stiffness–mean pressure curves for vessels and grafts; all curves were generated using a linear regression model. CPU, compliant poly(carbonate)polyurethane; ePTFE, expanded polytetrafluoroethylene

oscillating electrical circuit—diminishes flow pulsatility¹⁹ and perfusion efficiency²⁰, and in low-flow situations may lead to further flow stagnation and graft thrombosis. Disparity of compliance at the junction of graft and artery has been postulated to cause neointimal hyperplasia by stimulation of perianastomotic smooth muscle cells exposed to anomalous cyclical strain forces²¹ and to mitogens released by activated platelets²² trapped by anastomotic flow disturbance. Development of a compliant vascular graft for use in low-flow, infrapopliteal arterial bypass is thus a goal in the struggle to improve the disappointing

long-term patencies associated with the use of ePTFE and Dacron.

Attempts to fabricate compliant vascular grafts have involved elastomeric materials such as silicone rubber²³ and polyurethane²⁴. However, compliant prostheses must by necessity be biostable, as is the case with ePTFE and Dacron, if they are to be considered safe for clinical use. Polyether-based segmented urethanes are susceptible to oxidation reactions, catalysed by enzymes released during the inflammatory response, which can lead to surface fissuring and material degradation²⁵.

The authors have developed a vascular graft made from CPU that is not based on polyether segments using an innovative chemistry and stress-free fabrication process. It has been shown to resist oxidative and hydrolytic stress both *in vitro* and *in vivo*^{7,26}. The graft has a microporous honeycomb structure that readily facilitates pulsatile deformation. This paper concerns the quantification of the compliance properties of this new graft compared with those of artery and vascular grafts made from ePTFE and Dacron.

The elastic behaviour of the grafts and vessels was measured over a range of mean pressures. This was because arterial tissue is a heterogeneous material that does not obey Hooke's Law in response to cyclical blood pressure change. As such, it is said to be anisotropic, i.e. there is a non-linear relationship between the degree of radial deformation exhibited by arteries in response to an increase in intraluminal pressure^{11,20}. The distensile behaviour of an artery is not only governed by the driving change of the pulse pressure (i.e. systolic–diastolic pressure), but by the mean pressure about which the pulse pressure is operating. At low pressures the load is predominantly borne by highly distensible elastin fibres²⁷, but at high pressures it is transferred to the poorly elastic collagen fibres²⁸. Vein is also non-Hookean but, unlike artery, load is transferred to the collagen fibres at lower strain (pressure) because venous walls contain less elastin and smooth muscle. Consequently vein is incompressible when exposed to the higher mean pressures associated with arterial circulation. Prosthetic grafts do not exhibit this anisotropic pattern of behaviour and have more uniform pressure–compliance curves. When averaged over the entire pressure range, the mean compliances of CPU and artery appeared similar (mean(s.d.) 8.1(0.4) and 8.0(5.9) per cent per mmHg $\times 10^{-2}$ respectively). There was no significant difference between artery and CPU compliance at mean pressures of 30–60 mmHg, but increasing the pressure above this range caused compliance mismatch as arterial distensibility diminished: at 100 mmHg the compliances were 8.1(0.7) per cent per mmHg $\times 10^{-2}$ for CPU and 2.6(0.8) per cent per mmHg $\times 10^{-2}$ for artery ($P < 0.001$). It

Table 3 Outcome of analysis of variance comparison of compliance and stiffness value of expanded polytetrafluoroethylene, Dacron, vein and compliant poly(carbonate)polyurethane against artery with Bonferroni analysis

		<i>P</i>							
Pressure (mmHg)		Vein		CPU		Dacron		ePTFE	
Mean	Systolic/diastolic	C	β	C	β	C	β	C	β
30	70/10	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001	<0.001	<0.001
40	80/20	<0.01	n.s.	n.s.	n.s.	<0.001	<0.001	<0.001	<0.001
50	90/30	<0.01	<0.05	n.s.	n.s.	<0.001	<0.001	<0.001	<0.001
60	100/40	<0.001	<0.01	n.s.	n.s.	<0.001	<0.01	<0.001	<0.001
70	110/50	<0.05	n.s.	<0.001	n.s.	<0.001	<0.01	<0.001	<0.001
80	120/60	<0.01	<0.05	<0.001	n.s.	<0.01	<0.001	<0.001	<0.001
90	130/70	<0.01	n.s.	<0.001	n.s.	<0.001	<0.01	<0.001	<0.01
100	140/80	n.s.	n.s.	<0.001	<0.05	n.s.	n.s.	<0.01	<0.001

CPU, compliant poly(carbonate)polyurethane; ePTFE, expanded polytetrafluoroethylene; C, compliance; β , stiffness value; n.s., not significant

is arguable that compliant grafts destined for use in the relatively low-flow, low-pressure environment of the diseased infrageniculate arterial tree should preferentially match artery over lower, rather than higher, pressure ranges. Interestingly, the stiffness indices of artery and CPU remained similar over a more extensive pressure range (*P* not significant from 30 to 90 mmHg) than was the case for the relevant compliance values. While compliance describes the functional vascular distensibility in response to a change in blood pressure, arterial wall stiffness index β is less dependent on quantitative pressure change in describing the viscoelastic behaviour of an artery, and thus has been advocated as a more useful description of distensibility^{29,30}. Equivalence of stiffness between artery and CPU suggests that, notwithstanding the effect of pressure preload on arterial expansibility, the intrinsic elastic natures of CPU and muscular artery are similar.

As expected, ePTFE was considerably stiffer and less compliant than artery over the whole pressure range. The knitted Dacron grafts were similarly inelastic although the reduction in arterial distensibility at higher mean pressures meant that their respective compliance and stiffness indices were not statistically different at 100 mmHg.

The elastic behaviour of a vessel can be determined statically by measuring wall excursion during stepwise inflation of an intraluminal balloon, but this approach does not allow for the contribution that vessel or graft wall viscosity (i.e. inertia) makes upon the *in vivo* elastic response¹¹. The amount of radial movement (strain) that a vessel wall exhibits in response to a change in intraluminal pressure (stress) is also dependent upon the rate at which the pressure is applied, i.e. wall behaviour is viscoelastic. In order to fully characterize likely *in vivo* graft or vessel

viscoelastic behaviour, a dynamic approach was required. Thus, a pulsatile flow circuit, capable of supporting biological tissues, was designed to allow cyclical application of wall stress and the reproduction and manipulation of physiological flow parameters. An ultrasonographic echo-locked wall-tracking system was used to record changes in graft or vessel diameter over each pulsatile cycle; this method has been validated³¹⁻³³ and is associated with an intraobserver error of around 5 per cent for diameter measurement.

Both the anterior and posterior walls of the subject graft must be imaged for ultrasonographic wall tracking to be successful. It was noted initially that while CPU, Dacron and artery were readily imaged in this respect, the anterior wall of ePTFE was very echogenic and accurate depiction of the posterior wall was prevented. Degassing the graft in 70 per cent ethanol solved this problem and for purposes of consistency all graft types were treated similarly. Unlike Dacron, the ePTFE and CPU grafts do not require preclotting when used *in vivo*, as the pores are quickly sealed with fibrin and other elements of whole blood upon restoration of blood flow. However, using this *in vitro* system it became apparent that to avoid leakage of perfusate and prevent loss of intraluminal pressure, all graft types would need formal preclotting before mounting within the circuit. Presumably, a fibrin mesh can contribute to the structural strength of a preclotted graft and alter its intrinsic elastic nature, but the effect of preclotting upon the mechanical properties of these grafts was not studied.

Another potential criticism of the *in vitro* approach is that the data derived have limited applicability to the *in vivo* situation. *In vitro* studies may overestimate *in vivo* arterial elasticity, as the latter is also influenced by the degree to

which adjacent connective tissues tether arterial wall excursion³⁴. Furthermore, vessels experience a variable amount of smooth muscle tone *in vivo* secondary to sympathetic and humoral influences³⁵ not reproduced in the present *in vitro* system. The effects of overnight storage in Ringer's lactate on vessel tone were not investigated. However, the elastic behaviour of a vessel is determined primarily by its collagen and elastin content, and these constituents did not change appreciably during overnight storage. Finally, following implantation, porous prosthetic grafts become invaded by connective tissue elements that can fix the graft wall, thereby diminishing the compliance^{19,36} from that observed *in vitro*. Nevertheless, the *in vitro* approach allowed rigorous control of the physical forces to which the grafts or vessels were exposed; such a method is obligatory if any comparison of the material characteristics of different grafts and vessels is to be valid.

In summary, the new CPU vascular prosthesis provided a greater degree of graft-arterial compliance and stiffness match than either ePTFE or Dacron. This novel graft is now undergoing a pilot clinical trial in this institute and several other European centres for vascular reconstruction.

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Safety of a single duplex scan to exclude deep venous thrombosis

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Background: Guidelines advocate that a negative ultrasonographic scan needs to be followed by venography, or a repeat scan after 1 week, to detect potentially missed calf vein thrombosis. This study aimed to evaluate whether anticoagulation can safely be withheld on the basis of a single negative duplex scan in patients presenting with suspected deep venous thrombosis (DVT).

Methods: Duplex scan reports, case notes and questionnaires returned by general practitioners of patients with suspected DVT were analysed retrospectively. The main outcome measure was occurrence of an adverse thromboembolic event, a symptomatic DVT or a pulmonary embolism, within 3 months after a negative duplex scan.

Results: Some 537 patients had 706 leg scans performed, the majority because of leg symptoms or to look for indirect evidence of pulmonary embolism. Among 352 patients, who had 429 negative leg scans, four possible adverse events were identified. The rate of adverse outcome was therefore 1.1 per cent per patient and 0.9 per cent per leg.

Conclusion: Withholding anticoagulation in patients who had a single, complete, negative duplex scan is safe. A repeat scan should be performed if there is ongoing high clinical suspicion and considered in patients in whom the calf veins could not be visualized.

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Introduction

Venous thromboembolism remains a common cause of morbidity and death in surgical patients in spite of widespread use of antithrombotic prophylaxis. Vascular surgeons are confronted with the chronic complication of deep venous thrombosis (DVT), the post-thrombotic leg. The clinical diagnosis of DVT is unreliable and needs to be confirmed by an objective test. Venography is considered to be the gold standard but has been replaced in recent years by ultrasonography as the routine imaging modality in many centres^{1–3}.

Recently published guidelines have recommended that a negative ultrasonographic scan (compression or duplex) should be followed by either venography to detect deep calf vein thrombosis or repeat ultrasonography after 7 days to detect proximal extension of calf vein thrombosis⁴. This would increase the workload of radiology departments or vascular laboratories considerably.

In this hospital, duplex imaging is used in all patients referred with suspected DVT. Venography or serial imaging is not performed routinely after a negative test.

The objective of this study was to evaluate the safety of this practice.

Patients and methods

In a retrospective and descriptive study, all patients who had a duplex scan performed in a 12-month interval because of clinical suspicion of acute lower limb DVT were identified using a computerized database. The patients were referred from the community or within the hospital to the radiology department of a single district general hospital in Scotland with a catchment population of 220 000. Imaging was performed by consultant radiologists only, according to local protocols. Patients with a suspected DVT were added to the next consultant ultrasound list, usually within 2 or 3 h, or scanned as an emergency at the weekend. A 10–5-mHz linear or 7–4-mHz curved array transducer and a colour duplex ultrasound machine (HDI 3000, ATL, Bethel, CT, USA) were used. Attempts were made to visualize the deep veins of the leg using a combination of techniques to identify thrombus, including B-mode compression scanning, augmentation, colour and power imaging. The leg

was imaged while dependent and, where possible, thrombus was sought in distal (infrapopliteal) deep veins, posterior tibial, peroneal and calf muscle veins, as well as in the proximal leg veins.

The duplex scan reports were reviewed to determine the segments of the venous system examined, the presence and extent of any DVT, and any other findings. Some patients received anticoagulation between presentation and duplex imaging, depending on the delay and the degree of suspicion of DVT.

The case notes of all patients who had a negative duplex scan were evaluated for an adverse event occurring in the 3 months after the initial examination. Where there was insufficient information in the case notes a questionnaire was sent out to the general practitioner (GP). The two endpoints were a symptomatic DVT confirmed by a subsequent test and a pulmonary embolism or death that might have been related to pulmonary embolism. A primary scan was defined as an examination of a leg performed for the first time in a 3-month interval. The binomial distribution for proportions was used to estimate the confidence interval for adverse outcome rates.

Results

In a 12-month interval 537 patients with suspected DVT were referred for duplex imaging. A total of 706 leg examinations was performed; 669 of these were primary scans. The mean age of all patients was 63.7 (range 9–95) years. There was a slight female preponderance (57.2 per cent).

The majority of patients (74.1 per cent) were referred from the community, usually by a GP. The remainder (25.9 per cent) developed symptoms or signs suspicious of DVT while under treatment in hospital for another condition.

The majority of legs were examined because of symptoms and signs suggesting DVT (72.2 per cent) or to look for indirect evidence of pulmonary embolism (20.1 per cent), or both (5.2 per cent). Examination of the contralateral asymptomatic leg was not a common request (1.6 per cent). Few patients had a planned follow-up scan (0.8 per cent). Only one venogram was performed in the same 12 months, in a patient who had an equivocal duplex scan.

Of 669 primary scans, 165 (24.7 per cent) demonstrated the presence of DVT (*Table 1*). The rate of positive scans in patients referred from the community was almost identical to the rate in patients who were already hospitalized. The proximal extent of thrombus was most commonly in the femoral vein. In 29.1 per cent of the positive scans, thrombus was isolated in the deep calf veins. The calf veins were visualized in 58.6 per cent of the negative scans, in 23.4 per cent they could not be seen and in the remainder the

Table 1 Findings of venous duplex imaging (669 primary scans)

	No. of scans
Deep venous thrombosis	165 (24.7)
Iliac vein	22 (13.3)
Femoral vein	76 (46.1)
Popliteal vein	19 (11.5)
Calf veins	48 (29.1)
No deep venous thrombosis	504 (75.3)
Calf veins visualized	295 (58.6)
Calf veins not visualized	118 (23.4)
Calf veins uncertain	91 (18.1)

Values in parentheses are percentages

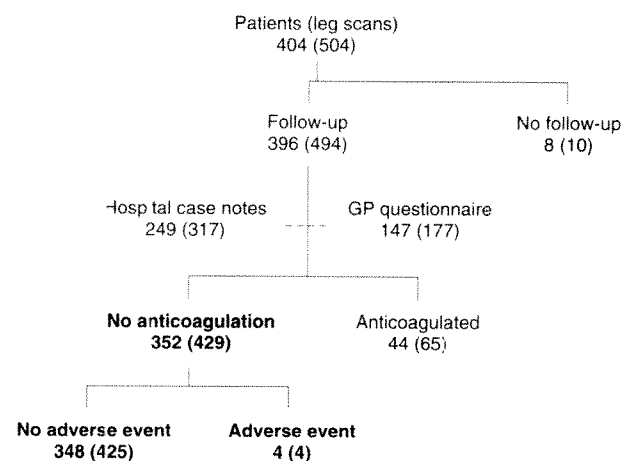


Fig. 1 Outcome of patients with negative duplex imaging for suspected deep venous thrombosis. GP, general practitioner

report did not specify whether or not the calf veins were examined. In 88 (17.5 per cent) of the 504 negative leg scans an alternative explanation for the leg symptoms or signs was demonstrated by the radiologist. Common findings included ruptured Baker's cyst (20 scans), superficial venous thrombosis (17) and oedema or haematoma (29). Less frequent but important diagnoses included pelvic mass (one), inguinal lymphadenopathy (four), sarcoma of the thigh (one), occlusive arterial disease (two) and popliteal artery aneurysm (one).

The outcome in the group of 404 patients who had 504 negative leg scans is shown in *Fig. 1*. Follow-up data could not be obtained in eight patients (ten legs), all of whom were visitors to the area. The negative follow-up rate was therefore 2.0 per cent. About two-thirds of the follow-up data were obtained from review of case notes and one-third from GP questionnaires. Some patients received long-term anticoagulation because of pulmonary embolism, DVT in the opposite leg, high clinical

Table 2 Adverse events after a negative venous duplex scan (352 patients, 429 leg scans)

No.	Sex	Age (years)	Primary condition	Primary event	Secondary event	Diagnosis	Outcome
1	Male	59	Pelvic recurrence of rectal carcinoma	Swollen leg	Progressive leg signs (day 4)	Popliteal-calf DVT	Died from primary condition (day 221)
2	Male	60	Cerebral infarcts, carcinoma of lung	Calf pain	Recurrent leg signs (day 30)	Iliofemoral DVT	Died from primary condition (day 51)
3	Male	84	Infective exacerbation of COAD	Calf pain (incomplete scan)	Recurrent leg signs (day 34)	Femoropopliteal DVT	Died from primary condition (day 75)
4	Female	66	Infected ipsilateral knee prosthesis	Calf pain (incomplete scan)	Chest signs (day 42)	Possible PE	No further chest signs

DVT, deep venous thrombosis; COAD, chronic obstructive airways disease; PE, pulmonary embolism

suspicion of DVT or a cardiac condition. In the group of 352 patients (429 leg examinations) who were not anticoagulated following a single negative duplex scan, four adverse events were identified within 3 months (Table 2). All four patients were treated in hospital for another condition and belonged to a moderate- or high-risk group for DVT. Three patients had progressive or recurrent leg signs and a DVT was revealed by a repeat duplex scan (two patients) or at autopsy (one). All three patients died from the primary condition. The fourth patient presented with chest symptoms 6 weeks after a negative scan and was anticoagulated as for a pulmonary embolism on the basis of moderate clinical and intermediate radiological (ventilation-perfusion scan) probability. In two of these patients the calf veins could not be visualized at the initial examination and this was stated positively by the radiologist in the report. Twenty-six patients with a negative scan died within the follow-up interval. Although the majority did not have a post-mortem examination their deaths could not be related to venous thromboembolism. The rate of adverse outcome was therefore 1.1 (95 per cent confidence interval 0.0–2.2) per cent per patient and 0.9 (0.0–1.8) per cent per leg examination.

Discussion

Venous thromboembolism is a common condition affecting patients in hospital but also seemingly healthy people in the community⁵. Clinical assessment can predict the probability of DVT but is not accurate on its own and needs to be combined with an objective test⁶. In the present study only 24.7 per cent of legs referred with suspicion of DVT had a positive examination, which is similar to other studies using ultrasonography as the diagnostic test^{7,8}. Venography has been regarded as the gold standard test for DVT^{1–3} but is invasive, and is associated with both minor and serious risks

owing to endothelial toxicity and adverse contrast reactions. Venography has a 2 per cent risk of causing a DVT⁹ and is uncomfortable for the patient; it involves the use of ionizing radiation, is expensive, time consuming, and has a significant rate of inadequate examination, as well as misinterpretation³.

Ultrasonography is non-invasive and is now used widely as the routine test for suspected DVT. The term 'ultrasound scan' has been used in the literature to cover several distinct techniques. Augmentation imaging relies on insonation of the femoral veins during calf compression to listen for a transmitted signal. Real-time scanning (B mode) uses compression of the vein to establish the presence of thrombus (an incompressible vein is assumed to contain thrombus). Duplex ultrasonography is a combination of pulsed-wave Doppler and real-time imaging that allows assessment of flow as well as direct visualization of echogenic material within the vein lumen. Colour and power Doppler techniques are useful adjuncts to the duplex ultrasonographic examination¹. Although ultrasonography is operator dependent, high sensitivity and specificity (exceeding 95 and 98 per cent respectively) have been reported for the diagnosis of DVT involving the proximal leg veins².

There is concern that ultrasonography may miss deep calf vein thrombi⁷. The clinical significance of calf vein thrombosis is controversial¹⁰. The risk of pulmonary embolism from isolated calf vein thrombosis seems negligible; however, a recurrence rate of 29 per cent and propagation rate into more proximal veins of up to 28 per cent have been reported^{11–13}. The accuracy of ultrasonography for the diagnosis of calf vein thrombosis has been highly variable in the few studies available. Sensitivity and specificity have ranged between 11 and 100 per cent and 90 and 100 per cent respectively². The rate of isolated calf vein thrombosis in the present study (29.1 per cent) compares with a rate of 12 per cent in a study using

venography as the diagnostic test¹⁴. This would suggest that a significant number of calf vein thromboses were not missed.

The argument for repeat ultrasonography or venography in patients with a negative scan is based on the potential risk of missing calf vein thrombosis that might propagate into more proximal veins^{4,7,15}. The incidence of thromboembolic complications after a single negative ultrasonographic scan in the present study was low (1.1 per cent per patient or 0.9 per cent per leg), even using the widest possible definition. One DVT was diagnosed within a week of the index scan because progressive leg signs mandated a repeat scan. Clearly a protocol using serial scans over 7 days would not have altered the outcome of this patient. The other two cases of DVT presented 4–6 weeks later and it is debatable whether these were missed or new. The patient with a possible non-fatal pulmonary embolism had an infected knee prosthesis and required multiple procedures as well as immobilization in the 6 weeks between the negative scan of the same leg and chest symptoms. A causal relation of the two events could not be excluded for the purpose of this study but is doubtful clinically. The rate of adverse outcomes was comparable to that in other reported studies using serial ultrasonographic imaging^{7,15}. All thromboembolic complications after a negative ultrasonographic scan occurred in moderate- or high-risk, hospitalized patients. In two of the four patients the calf veins could not be visualized and this was stated positively by the radiologist. No adverse event was identified in 296 patients (368 leg examinations) referred from the community.

Duplex imaging is currently the investigation of choice for patients with suspected DVT. Duplex imaging is non-invasive, highly sensitive and capable of demonstrating an alternative cause in a significant proportion of patients. From the present data, withholding anticoagulation in patients who had a single, complete, negative duplex scan appeared safe. A repeat scan should be done if there is ongoing high clinical suspicion of DVT. A further scan should also be considered in patients who had an incomplete scan (i.e. visualization of calf veins compromised) and no alternative diagnosis.

Post-thrombotic syndrome is another potential complication of missed DVT. Given the time necessary for this to develop, it is difficult to study, but there is no convincing evidence that isolated calf vein thrombosis leads to chronic venous insufficiency¹².

The large number of patients referred for imaging of deep veins and the relatively low prevalence of DVT in this population has initiated the search for alternative strategies. Using the D-dimer test in conjunction with assessment of clinical pretest offers the possibility of further refining the selection of patients for imaging¹⁶.

Acknowledgements

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Vasoactive and proliferative effects of parathyroid hormone and parathyroid hormone-related peptide on human vascular smooth muscle

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Background: Hyperparathyroidism is associated with an increased incidence of hypertension and cardiovascular disease. Experiments in rats suggest that this results from desensitization of the normally inhibitory effects of parathyroid hormone-related peptide (PTHrP) on vascular smooth muscle cells (VSMCs) by previous exposure to parathyroid hormone (PTH).

Methods: Isometric tension *in vitro* was measured in segments of vessels obtained at neck surgery from six normotensive patients with hyperparathyroidism and 12 eucalcaemic controls undergoing thyroid surgery. Vessels were precontracted with noradrenaline to allow the vasodilatory effects of PTH and PTHrP to be observed. Human VSMCs were cultured in 0.5, 5 and 15 per cent serum with or without PTH (10^{-11} to 10^{-7} nmol l⁻¹) and proliferation was assessed by cell counts after 14 days.

Results: Vasodilatation of arterial segments produced by both PTH 20 nmol l⁻¹ and PTHrP 100 nmol l⁻¹ did not differ significantly between control and hyperparathyroidism groups ($P > 0.08$, Mann-Whitney *U* test). Vasodilatation by PTHrP was not reduced by preincubation of vessels *in vitro* with PTH 50 nmol l⁻¹ for 1 h ($P > 0.36$, Wilcoxon test). No effects of PTH on serum-induced proliferation of human VSMCs were observed.

Conclusion: These data imply that homologous desensitization to PTHrP is not implicated in the pathogenesis of vascular disease in patients with hyperparathyroidism.

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Introduction

Hyperparathyroidism is associated with an increased incidence of hypertension and death from cardiovascular disease^{1–7}. The mechanisms for this remain unclear. However, cardiovascular morbidity may be related to the duration of hyperparathyroidism⁵ and its severity, as reflected by higher preoperative calcium levels⁵, increased weight of adenoma⁸ and higher postoperative levels of parathyroid hormone (PTH) in some patients⁷. Raised PTH levels are also found in other hypertensive disorders^{9–10}.

Despite this, PTH itself appears to act as a smooth muscle relaxant and produces dilatation of arterial segments *in vitro*^{11–15}. Similar effects are also produced by para-

thyroid hormone-related peptide (PTHrP)^{13–16}. This peptide is produced by vascular smooth muscle cells (VSMCs), particularly those stimulated by vasoconstrictors or mechanical stretch^{17–19}, and may therefore act as an autocrine or paracrine regulator of VSMC tone.

It has also been shown that preincubation of rat arterial segments with PTH for up to 90 min *in vitro* markedly reduces the acute vasodilatory response to subsequent application of either PTH or PTHrP (so-called homologous desensitization)¹⁵. Furthermore, changes in intracellular levels of cyclic adenosine 5'-monophosphate and calcium within isolated VSMCs, which mediate PTHrP-induced vasodilatation, are reduced by preincubation with PTH^{12–15,20–21}. These changes also influence VSMC proliferation^{16–22}, which has been

implicated in the pathogenesis of hypertension and atherosclerosis²³.

It has been postulated, therefore, that in patients with hyperparathyroidism chronic exposure to increased PTH levels contributes to vascular disease by impairing the inhibitory effects of PTHrP on VSMC tone and proliferation.

No previous studies have reported the effects of PTHrP on human vascular tissue, or their modulation by PTH. Therefore, these issues were examined using intact human vessels *in vitro*, including vessels from patients with hyperparathyroidism to seek evidence of desensitization induced by the hyperparathyroid state. The effects of PTH on serum-induced proliferation of isolated human VSMCs *in vitro* were also examined.

Patients and methods

Materials

Chemicals and media were obtained from Sigma (Poole, Dorset, UK). Peptides were human PTH(1–84) (purity 74 per cent) and human PTHrP(1–40) (purity 99 per cent).

Contractile responses of intact vessels

Ethics committee approval was obtained and informed consent given by all patients. Segments (2 cm) of anterior jugular vein and superior thyroid artery were obtained from patients undergoing neck exploration for hyperparathyroidism and from a control group of patients undergoing thyroid surgery for non-toxic goitre. The control group comprised 12 normotensive patients (ten women, two men; median age 49 years; median albumin-corrected calcium concentration 2.31 (range 2.19–2.59) mmol l⁻¹). The study group comprised six hyperparathyroid patients (five women, one man; median age 65 years), five with primary hyperparathyroidism and one with ('tertiary') renal hyperparathyroidism (median calcium level 2.71 (range 2.62–2.79) mmol l⁻¹ ($P < 0.01$ *versus* controls, Mann–Whitney U test); PTH concentration 103 (85 to more than 2000) ng l⁻¹).

Vessels were divided into 2–3-mm segments. The lumen of each segment was cannulated with stainless steel wires, and segments were mounted in a water-jacketed (37°C) oxygenated tissue bath in Krebs–bicarbonate buffer (Na⁺ 143 mmol l⁻¹, K⁺ 5.87 mmol l⁻¹, Cl⁻ 125.3 mmol l⁻¹, HCO₃⁻ 25 mmol l⁻¹, H₂PO₄⁻ 1.18 mmol l⁻¹, SO₄²⁻ 0.61 mmol l⁻¹, Ca²⁺ 1.29 mmol l⁻¹, Mg²⁺ 0.61 mmol l⁻¹, glucose 11.1 mmol l⁻¹, pH 7.4) and connected to an isometric force transducer coupled to a continuous graphical recording system. Vessels were incubated at a passive tension of 0.8–1.0 g for 90 min before the addition of vasoactive agents.

Vessel segments were precontracted with noradrenaline (ED₅₀ approximately 300 nmol l⁻¹) and responses to PTH and PTHrP were assessed by comparing separate 3-min contractions with noradrenaline alone to those with noradrenaline plus peptide with respect to maximal tension achieved and the area under each contraction curve (AUC) (using a Wilcoxon signed rank test for paired data). Between each contraction, vessels were washed three times and allowed to restabilize to the original baseline before further stimulation.

Noradrenaline contracted vessels with mean (s.d.) values of maximal tension and AUC of 0.46(0.24) g and 1.67(1.53) g min respectively for vein, and 0.52(0.30) g and 1.12(0.89) g min for artery. The within-pair coefficient of variation²⁴ for each of these values was 9.4, 9.4, 12.4 and 15.2 per cent respectively.

Concentrations of PTH up to 10⁻¹¹ mol l⁻¹ (normal serum concentration approximately 1–6 × 10⁻¹² mol l⁻¹) had no effect on either vein or artery segments (data not shown). Vasodilatation was, however, observed with PTH and PTHrP in the 10–100 nmol l⁻¹ concentration range. PTH was a little more potent than PTHrP, and data are shown for PTH 20 nmol l⁻¹ and PTHrP 100 nmol l⁻¹.

Proliferation of cultured human vascular smooth muscle cells

Human VSMCs were harvested and maintained in culture as described previously^{25–26}. Established cell cultures of venous (long saphenous vein harvested for peripheral bypass surgery, $n = 5$) and arterial (arterial segments adjacent to vein graft stenosis, $n = 1$) origin were studied at passages 2–3.

In each experiment VSMCs were seeded (10⁴ cells per well in 1 ml per well of Dulbecco's modified Eagle's medium (DMEM) plus 15 per cent fetal calf serum (FCS)) in 24-well plates, and incubated at 37°C in a humidified atmosphere of 5 per cent carbon dioxide in air. After 3 days cells were washed with phosphate-buffered saline and growth-arrested by incubation in DMEM with 0.5 per cent FCS. After a further 4 days, triplicate wells were harvested with trypsin and counted in an electronic particle counter (Coulter Electronics, Luton, UK). Cells in the remaining wells were replenished with DMEM and FCS at either 0.5, 5 or 15 per cent with or without PTH (human sequence 1–84) at concentrations of 10⁻¹¹ to 10⁻⁷ mol l⁻¹, and continued in culture with renewal of media (and PTH) every 3 days. After a further 14 days cells at each concentration of FCS and PTH were harvested and counted (each in triplicate for five experiments using venous VSMCs, and each in quintuplicate for one experiment using arterial VSMCs).

The stability of PTH during incubation was also assessed. PTH(1–84) 100 nmol l^{-1} was added to VSMCs incubated with DMEM with or without 15 per cent FCS, and samples were withdrawn at intervals of 5, 10, 15, 30, 60, 90, 120 min and 3, 5 and 24 h, and immediately frozen at -80°C before subsequent measurement of PTH by a two-site (1–34 and 44–68 regions) chemiluminometric immunoassay (Magic Lite assay; Chiron Diagnostics, Emeryville, CA, USA), recognizing only intact PTH.

Results

Contractile responses of intact vessels

Responses of vessels to short-term exposure to PTH 20 nmol l^{-1} and PTHrP 100 nmol l^{-1} are summarized in Tables 1 and 2. Neither peptide significantly influenced venous contraction. Arterial segments underwent vasodilatation in response to both peptides. This response was similar in vessels from patients with hyperparathyroidism compared with those from the control group.

Desensitization of the vasodilatory response to PTHrP was examined by assessing responses before and after incubation of arterial segments with PTH (50 nmol l^{-1} for 1 h, $n=6$). Median (95 per cent confidence interval) percentage inhibition by PTHrP of noradrenaline-induced contraction before and after PTH incubation was 21 (4–75) *versus* 36 (15–82) per cent for maximal tension ($P=0.36$, Wilcoxon test) and 36 (–3 to 100) *versus* 39 (–19 to 100) per cent for the AUC ($P=0.89$): preincubation with PTH did not influence subsequent relaxation by PTHrP 100 nmol l^{-1} .

Proliferation of cultured human vascular smooth muscle cells

In the presence of VSMCs (with or without FCS), the half-life of immunoreactive PTH was 1474 min. The PTH concentration of culture media (with or without FCS) was below the limit of detection of the assay.

For venous VSMCs mean(s.d.) values for proliferation indices (ratio of number of cells at day 14 to number of cells at day 0) were 1.77(0.64) with 0.5 per cent serum, 4.27(1.40) with 5 per cent serum and 7.77(2.49) with 15 per cent serum. Corresponding values for arterial VSMCs were 1.49(0.18), 3.75(0.16) and 7.21(0.37) respectively. Three-way analysis of variance demonstrated that variation in proliferation indices was influenced mostly by serum concentration ($F=6583$ for venous VSMCs, $F=2429$ for arterial VSMCs, $P<0.00001$, 2 d.f.) and to a lesser extent by variability between strains of VSMCs. However, PTH concentration did not significantly affect proliferation ($P>0.18$ for both

Table 1 Effects of parathyroid hormone and parathyroid hormone-related peptide on maximal tension of vessel segments

	Ratio of contraction with NA plus peptide : NA alone			
	PTH (20 nmol l^{-1})	P^*	PTHrP (100 nmol l^{-1})	P^*
Control vein	1.05(0.91–1.17)	0.12	1.14(0.92–1.75)	0.22
Control artery	0.81(0.40–0.90)	0.005	0.75(0.35–1.00)	0.07
HPT artery	0.88(0.66–1.01)†	0.12	0.76(0.59–0.85)‡	0.028

Values are median (95 per cent confidence interval), ratios below 1 represent vasodilatation. HPT, hyperparathyroidism; NA, noradrenaline; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide. **Versus* NA alone (Wilcoxon test), † $P=0.17$, ‡ $P=0.87$ *versus* control artery response (Mann–Whitney *U* test)

Table 2 Effects of parathyroid hormone and parathyroid hormone-related peptide on area under contraction curves of vessel segments

	Ratio of contraction with NA plus peptide : NA alone			
	PTH (20 nmol l^{-1})	P^*	PTHrP (100 nmol l^{-1})	P^*
Control vein	1.02(0.86–1.16)	0.44	1.10(0.76–1.63)	0.36
Control artery	0.45(0.28–0.83)	0.003	0.61(0.36–0.75)	0.03
HPT artery	0.64(0.50–0.99)†	0.048	0.61(0.44–0.83)‡	0.028

Values are median (95 per cent confidence interval); ratios below 1 represent vasodilatation. HPT, hyperparathyroidism; NA, noradrenaline; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide. **Versus* NA alone (Wilcoxon test), † $P=0.08$, ‡ $P=0.75$ *versus* control artery response (Mann–Whitney *U* test)

venous and arterial VSMCs), either under basal conditions or following serum stimulation. These results are summarized in Fig. 1.

Discussion

The hypothesis examined in this study was that PTHrP inhibits the contraction and proliferation of VSMCs induced by stimuli such as noradrenaline, and that prolonged exposure to PTH impairs this inhibitory effect.

Direct measurement of isometric tension in vessel segments demonstrated that human superior thyroid arteries do indeed respond to PTH and PTHrP by vasodilatation. The doses of peptides that produced this response, and the degree of dilatation achieved, were similar to those observed in several other studies that have examined many vessels from various animal species^{12–13,15–18}. In one study, which examined the effects of PTH on human vessels¹¹, PTH 100 nmol l^{-1} produced 80 per cent relaxation

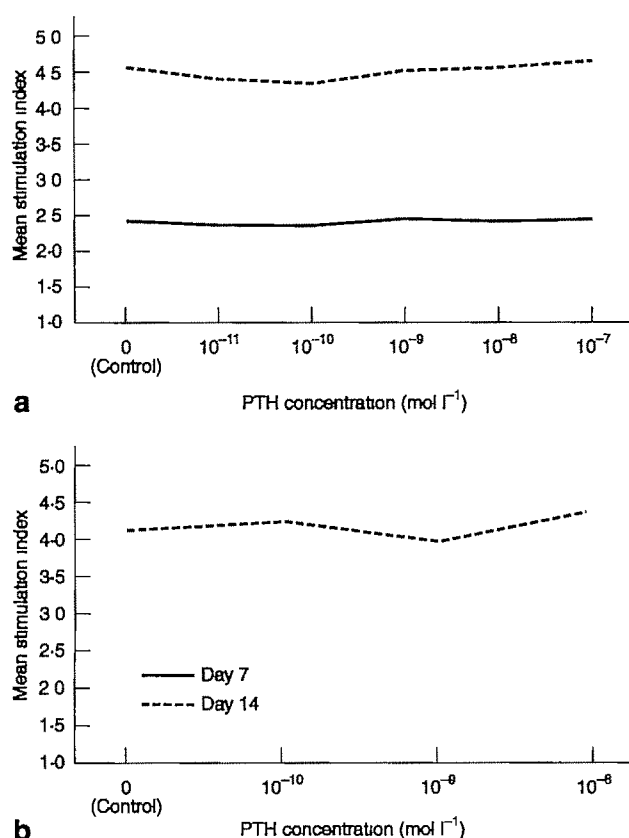


Fig. 1 Effects of parathyroid hormone (PTH) on the proliferation of **a** venous and **b** arterial vascular smooth muscle cells (mean stimulation index, three-way analysis of variance)

of middle cerebral arteries. This study did not, however, examine the effects of PTHrP, nor did it investigate desensitization by prolonged exposure to PTH.

The effective doses of PTH and PTHrP in all these studies are several orders of magnitude greater than the serum PTH concentration in humans, although this may still be consistent with a physiological role of PTHrP as a paracrine or autocrine factor in the regulation of VSMC tone, as local concentrations of PTHrP in the vessel wall may conceivably be this high. The consistent vasodilatory response between diverse animal species argues in favour of such a hypothesis.

Relaxation of rat arterial segments by PTHrP is reduced by preincubation *in vitro* with PTH 30–100 nmol l⁻¹ over 40 min¹⁵. In the present study using human arteries, however, vasodilatory responses to PTHrP were not significantly impaired by incubation with PTH 50 nmol l⁻¹ for 1 h.

In addition, arterial relaxation by PTH and PTHrP was similar between vessels from hyperparathyroidism and

control groups. This latter finding may conceivably have been due to a type II statistical error, as the number of patients in each study group was relatively small. In rat studies, however, desensitization by PTH reduced subsequent vasodilatation by over 50 per cent of baseline response¹⁵. The close similarity in responses between hyperparathyroidism and control groups in the present study therefore makes it unlikely that such a major desensitization effect is present.

It is, however, possible that desensitization may occur only in a subset of patients with hyperparathyroidism, i.e. those who become hypertensive. In this study none of the patients with hyperparathyroidism was hypertensive, so that such a selective desensitization effect may have been missed.

None the less, the combined findings that arterial vasodilatation by PTHrP is similar in patients with hyperparathyroidism and in controls, and is unaffected by preincubation *in vitro* with high concentrations of PTH, imply that homologous desensitization of vasodilatory responses, as observed in rats, does not occur to a significant degree in humans.

The reported effects of PTH and PTHrP on VSMC proliferation have been variable, some studies showing inhibition of DNA synthesis and others no influence of these peptides^{16–19,22–27}. The assessment of proliferation by changes in DNA synthesis may be confounded by the production of polyploid cells²³, and in the present study, therefore, cell counts were used directly to measure VSMC replication. The effects of PTH were studied on serum-stimulated VSMCs, as serum stimulation upregulates PTHrP production by VSMCs²⁷.

Owing to limited availability of arterial VSMCs at the time of this study, only a single experiment was performed using arterial VSMCs, which limits the conclusions that can be drawn. However, while both arterial and venous VSMCs demonstrated a normal proliferative response to serum stimulation, no effects of PTH on baseline or serum-induced proliferation could be detected. Further studies using arterial VSMCs would be necessary to investigate this issue fully, but a major effect of PTH seems unlikely.

In conclusion, PTH and PTHrP inhibited noradrenaline-induced contraction of human superior thyroid arteries, but did not influence contraction of anterior jugular veins. Arterial relaxation by PTHrP was similar to that observed in other animal species, was not reduced by preincubation *in vitro* with PTH, and was of similar magnitude in eucalaemic and hyperparathyroid groups. If superior thyroid artery responses to PTH and PTHrP reflect those of resistance vessels (and the close similarity of their responses to those of resistance vessels in all other studies supports this premise), these findings do not support the concept that homologous

desensitization of VSMCs to the effects of PTH and PTHrP is responsible for hypertension and cardiovascular morbidity in hyperparathyroidism.

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Experimental model of anorectal transplantation

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Background: Anorectal transplantation with pudendal nerve anastomosis after rectal excision is a possible strategy that would avoid a colostomy and recreate potentially normal anorectal function. This study investigates the technical feasibility of anorectal transplantation with pudendal nerve and inferior mesenteric artery and vein anastomosis in a porcine model.

Methods: Four female pigs (22–42 kg) provided donor anorectum for four male recipients (29–39 kg) under standard general anaesthesia. The donor operation involved abdominoperineal excision of rectum (APR) taking the anal sphincter, pudendal neurovascular bundle and inferior mesenteric vessels. The recipient underwent APR, transperineal introduction of the donor graft, anastomoses of the rectum, inferior mesenteric vessels and pudendal neurovascular bundle, and perineal closure. Recorded variables were duration of each step of transplantation, ischaemic time, dimensions of anastomosed structures and postoperative graft viability. Animals were killed at 24 h, the state of the graft was noted and tissue was taken for confirmatory histology.

Results: Mean operation time was 372 (range 303–435) min. Mean ischaemic time was 118 (100–130) min. Before death, observation at laparotomy revealed two pink grafts, one slightly dusky but healthy graft and one outright failure, reflecting the state of the mesenteric vessels, which were patent in three and thrombosed in one. Histological examination showed no difference between control biopsies and the three cases with satisfactory mesenteric flow. Gross ischaemia was present histologically in the failed case.

Conclusion: Anorectal transplantation is technically feasible in a pig model. Longer-term studies are now needed to assess return of function and overcome rejection issues.

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Introduction

The quest for anal continence after abdominoperineal excision of the rectum has led a number of surgeons to create a neoanus reconstructed from smooth muscle^{1,2}, transposed autologous skeletal muscle, either wrapped passively^{3,4} or electrically stimulated^{5–7}, or an artificial anal sphincter⁸. Clinical results have not been altogether satisfactory, partly because these methods were intended to replicate the anal sphincteric component of continence, reminiscent of a Thiersch implantation.

Anal continence is not just the result of contractile activity in the anal sphincter, but also depends on good sensation, reasonable capacity, and a colon and rectum that are neither too active nor too inert. Furthermore, the ability to be continent and the ability to evacuate are to some extent mutually antagonistic. This means that many of the above

surgical attempts to restore continence have been bedevilled by defaecatory problems because the patient has no idea when the rectum is full, and because contractile rectal activity and deactivation of whatever device is being used to control continence are not coordinated.

Anorectal transplantation should have the potential to solve a number of the above problems. Parts designed for a specialized purpose would seem on first principle to have a better chance of restoring best function compared with transposed muscle or implanted plastics, and the pudendal nerve, being a mixed motor and sensory nerve, should be able to restore sensation and perhaps anorectal reflexes. Furthermore, there is a case for organ transplantation for quality of life reasons alone, as has been exemplified by a report of a human laryngeal graft⁹. However, surgical access and strategy seem complex.

This study tested whether anorectal transplantation with pudendal nerve and inferior mesenteric artery and vein

anastomosis is technically possible in a short-term pig model.

Materials and methods

Personal and project licences for this study were granted by the Home Office to comply with the 1986 Animal Act. Preliminary cadaveric dissection in Large White Landrace pigs revealed that females had a well developed external sphincter muscle complex surrounding the anal canal and vagina, in contrast to males, in which the muscle was less bulky and encircled the anal canal only. In view of this peculiar anatomy, and ease of operation, four females (22–42 kg) provided donor anorectum to four recipient males (29–39 kg), having received premedication (xylazine 1 mg/kg and ketamine 5 mg/kg) 1 h before standard general anaesthesia (1–2 per cent halothane in 4 litres oxygen and 1 litre nitric oxide per min). Intravenous access was established in each recipient and 4.3 per cent dextrose/saline was given at a rate of 100 ml/h during and after transplantation.

Donor operation

Commencing in the left lateral position, a circumanovaginal incision was extended on both sides in a posterior lateral direction (*Fig. 1*). Preliminary cadaveric dissections had shown that mobilization between the rectum and coccyx, with detachment of the gluteus maximus muscle

along the incision margin, provided optimal exposure of the pudendal neurovascular bundle arising from the lateral pelvic wall. The external anal sphincter around both anus and vagina was dissected free and detached from the pubic bone (*Fig. 2*). The animal was then placed in the supine position and laparotomy with division of the symphysis pubis was performed. The inferior mesenteric artery and vein were prepared for division and the operation was suspended while the recipient was prepared. When this was accomplished, intravenous heparin 200 units per kg body-weight was given, and the pudendal structures were divided as far proximal as possible to facilitate subsequent reanastomosis in the recipient. The colon was then transected, followed by division of the inferior mesenteric artery and vein, releasing the specimen (*Fig. 3*). Bench dissection was then performed to detach the vagina from the donor specimen. The mesenteric artery was cannulated and perfused with 200 ml heparinized saline (5000 units heparin in 1000 ml normal saline) and preserved at 0–4° C to await transplantation.

Recipient operation

The perineal phase was similar to the donor operation, except instead of dealing with vagina, these pigs being male, the external anal sphincter encircling the anal canal was stripped free from the cavernosum muscle which was preserved. The abdominal phase omitted division of the pubic symphysis. The next steps were heparinization of

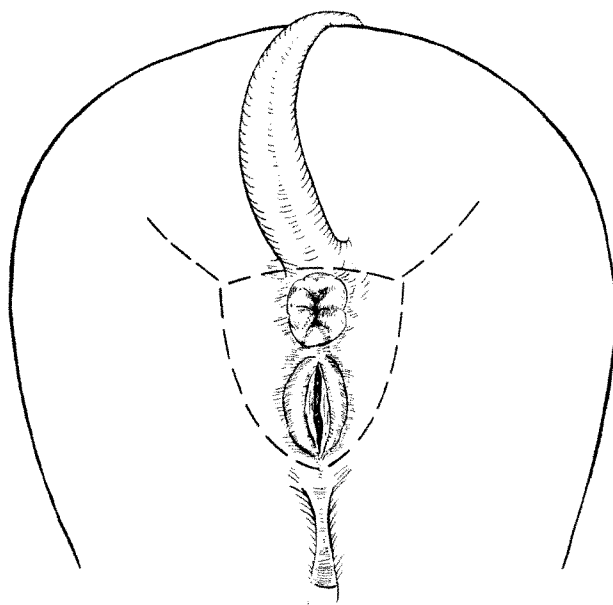


Fig. 1 Exposure of the perineum and circumanovaginal incision

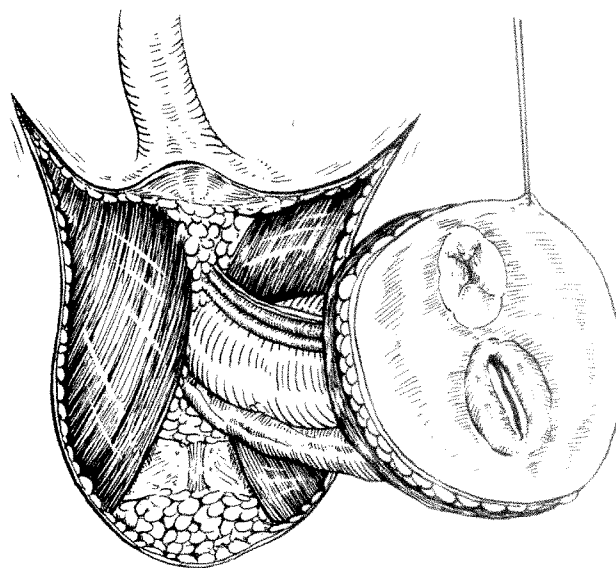


Fig. 2 Dissection *en bloc* of the anorectum, pudendal neurovascular bundle, vagina and uterus

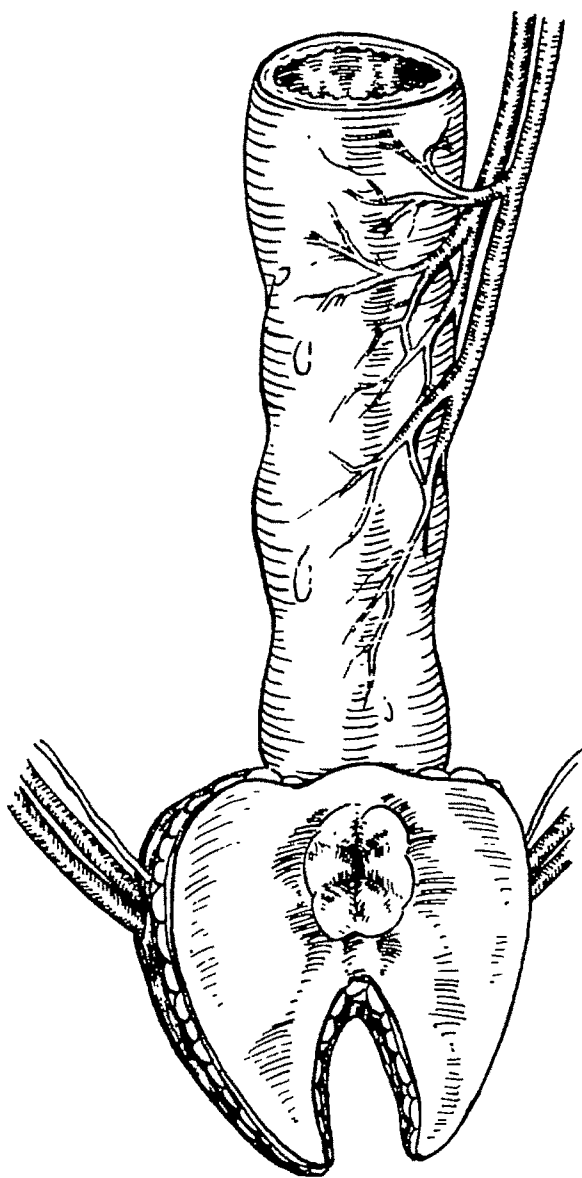


Fig. 3 Donor anorectal graft

recipient (200 units/kg); transperineal introduction of the anorectal graft; rectal anastomosis at the proximal end (single layer of interrupted 3/0 polyglactin) to stabilize the graft before microsurgical anastomosis of inferior mesenteric artery and vein (10/0 nylon in all pigs); laparotomy wound closure; microsurgical pudendal artery anastomosis (10/0 nylon in two pigs); bilateral pudendal nerve anastomosis (10/0 nylon by epineural technique in three pigs); and closure of the perineum (3/0 prolene) (*Fig. 4*). After transplantation, all recipient animals were given intramuscular analgesia (carprofen 4 mg/kg) every 4 h.

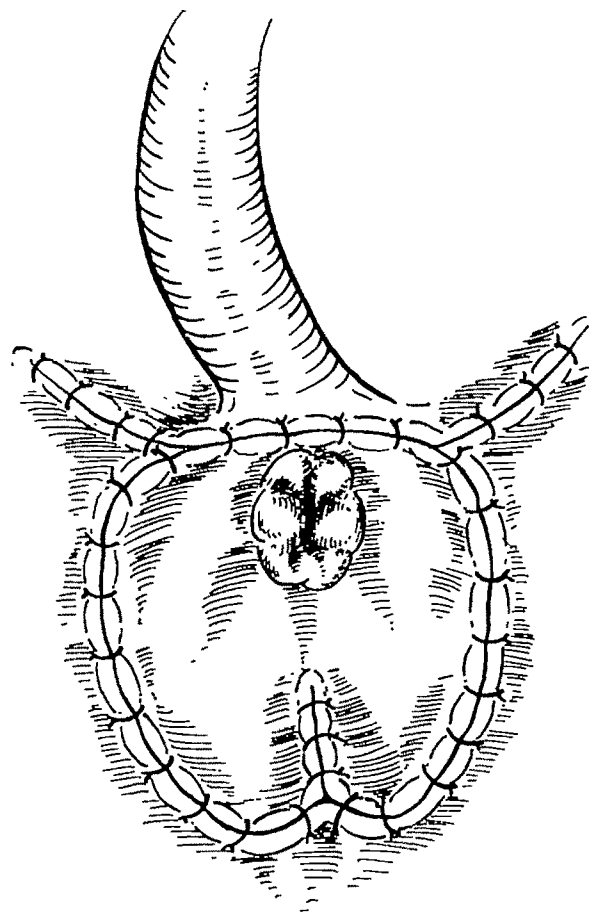


Fig. 4 Closure of perineal wound in recipient

Recorded variables

The duration of each step of the operations and ischaemic times were noted. The sizes of the various anastomosed structures (vein, artery and nerve) were measured with a millimetre grid scale (Ethicon, Edinburgh, UK) using a microscope at $\times 10$ magnification (OPMI-6; Carl Zeiss, Oberkochen, Germany). The subsequent condition and colour of the grafted skin was observed at regular intervals after operation. All animals were killed at 24 h, at which time the state of the various neurovascular anastomoses was noted and tissue (skin, muscle and mucosa) was taken for histological examination. These specimens were fixed in 10 per cent formalin, processed routinely, embedded in paraffin and cut into 5- μ m sections before staining with haematoxylin and eosin. The excised anorectum in the recipient animal provided control specimens.

Results

Total operation times (donor preparation plus recipient preparation plus transplantation time) ranged from 303 to

435 (mean 372) min. The mean ischaemic time was 118 min (Table 1). The recorded dimensions of artery, vein and nerve are given in Table 2.

All animals survived until being killed at 24 h. Observation of the graft before harvesting showed one outright failure, one slightly dusky and two pink and healthy grafts. These results mirrored the state of the mesenteric artery and vein anastomoses at 24 h, which were technically satisfactory in three and thrombosed in one. There were two pudendal vessel anastomoses and neither was satisfactory at 24 h.

Histological analysis at 24 h in the three pigs with satisfactory inferior mesenteric flow showed no difference to control biopsies (Fig. 5). Gross ischaemia was present histologically in the failed case.

Discussion

Anorectal transplantation is technically feasible in a porcine model. Although the operating times are lengthy, they

Table 1 Duration of steps in anorectal transplantation

Transplantation	Donor preparation (min)	Recipient preparation (min)	Ischaemic time (min)	Transplant time (min)
I	105	110	130	160
II	75	135	120	225
III	135	110	120	130
IV	100	95	100	108
Mean(s.d.)	104(25)	113(17)	118(13)	156(51)

Table 2 Donor and recipient dimensions of mesenteric vessels and pudendal nerve

Transplantation	Mesenteric artery (mm)		Mesenteric vein (mm)		Pudendal nerve (mm)	
	Donor	Recipient	Donor	Recipient	Donor	Recipient
I	2.0	1.5	2.5	1.3	2.2	1.8
II	2.0	2.0	1.5	3.3	—	—
III	2.0	1.3	2.5	1.0	1.5	1.5
IV	2.3	1.2	1.5	1.5	1.9	1.6
Mean	2.1	1.5	2.0	1.8	1.9	1.6

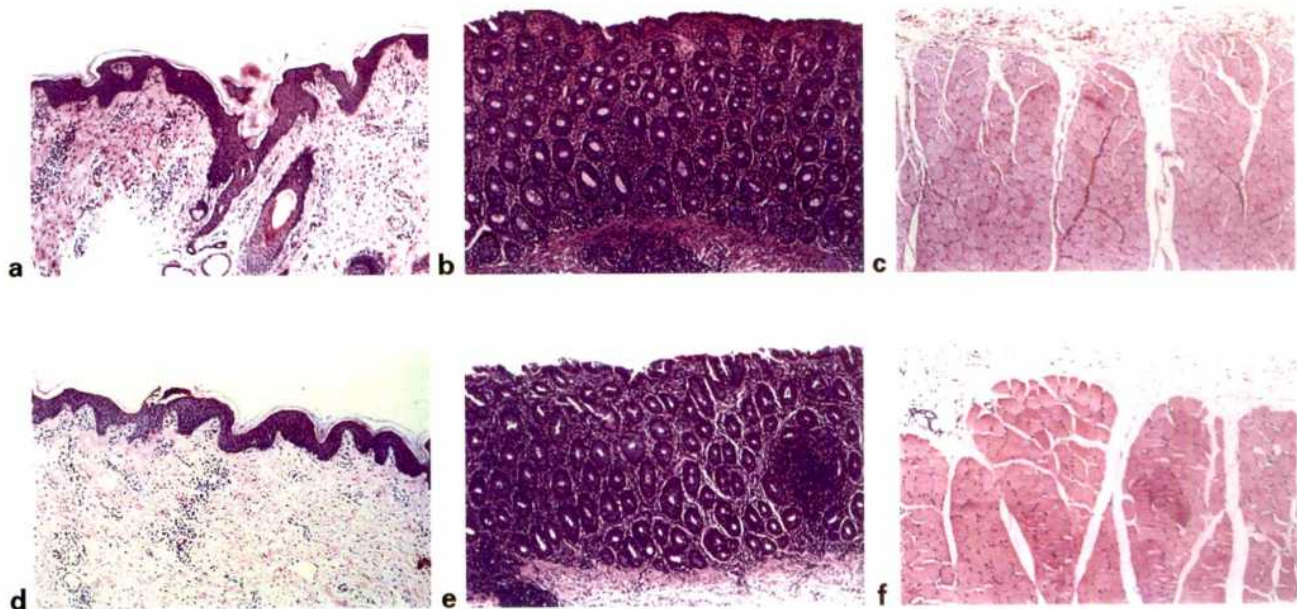


Fig. 5 Histological appearance of skin (a,d), mucosa (b,e) and muscle (c,f) in control (a,b,c) and transplanted (d,e,f) grafts

should shorten both with experience and if two surgical teams worked in parallel.

Pudendal artery and vein anastomoses were unsuccessful in the two pigs in which they were attempted, probably for technical reasons. The outright organ failure was caused by mesenteric arterial thrombosis, attributable to technical problems encountered with anastomosis during transplantation.

In the two animals in which pudendal vascular anastomosis was not performed, histological examination showed no sign of ischaemia at the radial margins of the transplanted sphincter so it is likely, at least in the pig, that the inferior mesenteric vessels are sufficient for good tissue viability, even at the margin. This is not surprising, as this area is a known watershed between the portal and systemic circulations, but confirmation in humans from postresectional angiographic studies would be reassuring should clinical transplantation become feasible in the future.

Recent interest has been generated from data in animal studies^{10,11} and from a clinical case report¹² of skeletal muscle neosphincters which behave like the native sphincter after cross-innervation of their nerve supply with the pudendal nerve. This novel approach indicates that the pudendal nerve may be crucial in attempts to restore normal physiological neosphincter function.

From first principles, nerve regeneration should be possible in a mixed nerve (autonomic, sensory and motor) of this size anastomosed microsurgically. However, adequate exposure of sufficient length of recipient nerve through careful meticulous dissection is obligatory, if successful end-to-end neural anastomosis without tension is to be achieved.

It was discovered from preliminary cadaveric dissections in this animal that a perineal as opposed to an abdominal approach provided best exposure of the pudendal neurovascular bundle. In one animal, unexpected division of the nerve trunk into multiple small fibres high in the pudendal canal, coupled with difficult access, made it impossible to isolate a suitable nerve for anastomosis with the pudendal nerve of the anorectal graft. This highlights the role potential anatomical anomalies involving the pudendal nerve¹³ may have should clinical anorectal transplantation ever be attempted.

These operations were performed simply to supply proof in principle that anorectal transplantation is a reasonable goal. In this short-term model, animals did not receive antibiotic or immunosuppressive therapy, a reasonable strategy given that the earliest signs of acute rejection may take up to a week to develop in the colon¹⁴. It is likely that the diminished colon antigenicity compared with small bowel is due to the relative paucity of lymphoid tissue¹⁵. Nevertheless, considerable further work will be needed to

assess return of function, prevent sepsis and to study and overcome rejection issues before anorectal transplantation can be considered in humans.

There will undoubtedly be sceptics. However, they should remember that, for many, particularly in other parts of the world, the prospect of anorectal amputation for cancer and a permanent colostomy is so awful that they are prepared to die rather than accept it and be cured. For these patients, the prospect of clinical anorectal transplantation might reasonably be considered lifesaving. For others, the recent clinical application of laryngeal transplantation⁹ heralds a new era that accepts that transplantation can be performed for quality of life reasons alone¹⁶.

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Rapid rehabilitation in elderly patients after laparoscopic colonic resection

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Background: Introduction of the laparoscopic surgical technique has reduced hospital stay after colonic resection from about 8–10 to 4–6 days. In most studies, however, specific attention has not been paid to changes in perioperative protocols required to maximize the advantages of the minimally invasive procedure. In the present study the laparoscopic approach was combined with a perioperative multimodal rehabilitation protocol.

Methods: After laparoscopically assisted colonic resection, patients were treated with epidural local anaesthesia for 2 days, early mobilization and enteral nutrition. Routine use of morphine and traditional tubes, drains and prolonged bladder catheterization was avoided.

Results: Laparoscopic resection was intended in 50 consecutive patients, of median age 81 years. The conversion rate to open resection was 22 per cent. In patients in whom the procedure was completed laparoscopically the median hospital stay was 2.5 days; defaecation occurred in 92 per cent of patients within 3 days. Patients were mobilized for more than 8 h daily from day 2.

Conclusion: Recovery after colonic surgery was improved considerably by combining the use of a laparoscopic technique with a multimodal rehabilitation protocol of pain relief, early mobilization and oral nutrition.

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Introduction

The indications for laparoscopic colonic resection remain controversial¹, and data from four randomized studies have shown only slight improvements in short-term morbidity and hospital stay^{2–6}. However, a common feature of both the randomized^{2–6} and non-randomized^{7–9} comparisons between laparoscopic and open colonic resection is that the general perioperative care protocol has not been adjusted to take account of recent scientific data on the use of optimal pain relief, which facilitates early mobilization, reduces postoperative ileus and permits early enteral nutrition^{10,11}. Moreover, most studies have not avoided routine use of gastrointestinal tubes, drains and prolonged urinary bladder catheterization^{10,11}. Interestingly, hospital stay has been reduced to between 2 and 5 days in non-randomized series of open colonic resection with revision of the perioperative care protocol and use of multimodal rehabilitation with optimal pain relief, early mobilization and nutrition^{12–15}. These results compare favourably with laparoscopic series that have employed traditional postoperative care

protocols^{2–9}. In a preliminary study of eight elderly and/or high-risk patients who underwent laparoscopic colonic resection, multimodal rehabilitation with continuous epidural analgesia, enforced early mobilization and enteral nutrition decreased hospital stay to 2–3 days¹⁶. The present study represents the cumulative experience in 50 consecutive elderly or high-risk patients with intended laparoscopic colonic resection combined with this postoperative rehabilitation protocol.

Patients and methods

Patients

Fifty consecutive elderly or high-risk patients scheduled for elective colonic resection in the years 1994–1996 were studied. Patients with malignant disease were included if they were aged at least 75 years, or 70 years or more and receiving treatment for chronic cardiopulmonary disease. Patients with benign disease were included if they were aged 70 years or more. Furthermore, inclusion required that

patients were self caring and admitted directly from home. Patients with tumours in the transverse colon or rectum were not included.

All patients were informed orally and in writing about the laparoscopic procedure and the postoperative protocol of epidural analgesia, early feeding and mobilization, and the expected discharge on day 2 after operation, provided that all organ functions were normalized. Preoperative mechanical bowel preparation was performed with macrogol 3000 balanced electrolyte solution (hospital pharmacy product). A single peroperative dose of antibiotics (cefuroxime and metronidazole) was given intravenously.

Anaesthesia and postoperative analgesia

A thoracic epidural catheter was inserted at T7–T9 and 6–9 ml 0.5 per cent bupivacaine was administered before operation. Thereafter general anaesthesia was induced by midazolam 0.15 mg/kg, fentanyl 0.1–0.25 mg and enflurane and nitrous oxide–oxygen. The epidural blockade was maintained with 0.5 per cent bupivacaine 4 ml/h during operation and continued after operation for 48 h with 0.25 per cent bupivacaine 4 ml/h. At the end of surgery 20 ml 0.25 per cent bupivacaine was injected beneath the fascia and subcutaneously in the largest incision. After operation, oral tenoxicam 20 mg or paracetamol 2 g 12 hourly was given daily for 6 days. Rescue analgesia included ibuprofen 600 mg every 8 h. Opioids were not given routinely in order to avoid cerebral and bowel motility side-effects. Intraoperative intravenous fluid was restricted to a maximum of 1500 ml, unless bleeding indicated otherwise.

Surgical procedures

Colonic resections were performed using a laparoscopically assisted technique as described previously¹⁶.

Postoperative care protocol

Gastrointestinal tubes were not used after operation. Oral feeding was initiated within a few hours of operation with fluids up to 1000 ml, including two protein-enriched drinks in the afternoon or evening of operation. From day 1 after operation enteral nutrition with solid food and four protein drinks daily plus free fluid intake aiming at at least 2000 ml was initiated. The urinary bladder catheter was removed on the morning after operation. Mobilization was enforced according to a fixed schedule aiming at 2 h on the day of surgery, 6 h on the first day and 8 h or more from day 2. Cisapride 20 mg was given every 12 h. The epidural catheter was removed before noon on the second day and discharge planned that afternoon (approximately 48 h after opera-

tion). A consultation in the outpatient clinic was arranged 10 days after operation for removal of stitches, information on histological findings and registration of data.

Pain, nausea and fatigue were recorded from days 1 to 10 using a four-point scale (0–3 representing none, slight, moderate and severe respectively). The need for additional analgesics, oral intake, vomiting, defaecation and duration of mobilization were recorded for 10 days after operation. After discharge the patients completed a specific questionnaire recording these variables. Registration of complications and need for rehospitalization was recorded for the first 30 days after operation.

The patients received written information and the telephone numbers of the surgeons responsible and the department. One month after operation patients were asked whether they were content with the regimen, including pain management and early discharge from hospital.

Results

Fifty patients with a median age of 81 (range 70–93) years were included. Five patients aged between 70 and 75 years were included as they had benign disease and/or severe cardiopulmonary disease. Seventeen patients were American Society of Anesthesiologists (ASA) grade I, 25 patients ASA II and eight patients ASA III. Twenty-six patients were receiving medical treatment for cardiovascular and/or pulmonary disease. Of 45 patients with malignant disease, 25 had Dukes' B, 17 Dukes' C and two had Dukes' 'D' lesions, and one patient had colonic stenosis due to ovarian cancer (not diagnosed before operation). The operative procedures performed are listed in Table 1. Thirty-nine operations were completed laparoscopically while 11 (22 per cent) needed conversion to an open procedure because of tumour invasion of neighbouring organs, unclear anatomy, ovarian cancer or an intraoperative tear in the anastomotic line following removal of the

Table 1 Surgical procedures performed in 50 elderly patients (median age 81 years) who underwent intended laparoscopic colonic resection

Procedure	Completed laparoscopically	Converted to open procedure	Total
Right hemicolectomy	24	2	26
Left hemicolectomy	4	1	5
Sigmoid resection*	11	7	18
Ileotransversostomy	0	1	1
Total	39	11	50

*Synchronous small bowel resection (two), hysterectomy and salpingo-oophorectomy (one)

Table 2 Reasons for conversion and postoperative course in 11 patients whose operation was converted to open surgery

	<i>n</i>
Intended operation	
Left hemicolectomy	1
Sigmoid resection	7
Right hemicolectomy	3
Reasons for conversion	
Cancer growth into neighbouring organs	6
Unclear anatomy	2
Technical difficulty	1
Ovarian cancer with sigmoid stenosis	1
Rectovesical fistula (diverticulitis)	1
Postoperative complications	
Colonic necrosis	1
Anastomotic leakage	1
Duodenal ulcer	1
Hospital stay (days)	
Uncomplicated cases	10 (5–15)*
Complicated cases†	37 and 64

*Values are median (range); †one patient with disseminated disease stayed in hospital until death 75 days after operation

Table 3 Postoperative gastrointestinal function in 39 elderly patients (median age 81 years) after laparoscopic colonic resection

	No. of patients		
	Day 1	Day 2	Day 3
Nausea	3	2	2
Vomiting	3	1	1
Oral intake >2000 ml/day	26	34	n.a.
Defaecation	29	34	36

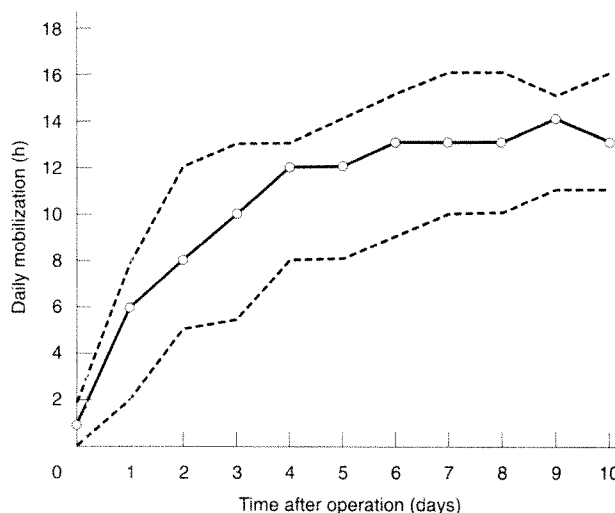
Three patients underwent reoperation in the early postoperative period. n.a., Data not available

Table 4 Postoperative complications in 39 elderly patients (median age 81 years) after laparoscopic colonic resection

	No. of patients
Complications	8
Anastomotic leak	2
Small bowel perforation	1
Mechanical bowel obstruction	3
Wound haematoma	1
Renal dysfunction	1
Death	2

surgical stapler in one patient. The postoperative course of the patients whose operation was converted is shown in *Table 2*.

In the 39 patients in whom the operation was completed laparoscopically, the median duration of operation was 180 (range 120–270) min and the median length of the

**Fig. 1** Median (range) postoperative mobilization in 36 elderly patients (median age 81 years) after completed laparoscopic colonic resection (three patients were excluded because of reoperation in the early postoperative period)

abdominal incision was 7 (range 4–12) cm. Median intra-operative blood loss was 50 (range 0–200) ml.

Gastrointestinal function

Recovery of gastrointestinal function is shown in *Table 3*. Most patients operated on laparoscopically had defaecation within 48 h of operation. Thirty-four of the 39 patients had an oral intake of at least 2000 ml within 48 h of operation. Three patients had reoperation in the early postoperative period (*Table 4*).

Pain, fatigue and mobilization

The median postoperative pain score after discharge was 1 (slight), and only five patients in the laparoscopic group took morphine tablets (10 mg) within the 10-day postoperative period. Postoperative mobilization was normalized early (*Fig. 1*). The median fatigue score was 1.5 (range 0–2) during the first 6 days and thereafter 0.5 (range 0–2).

Hospital stay

Twenty-six of the 39 patients operated on laparoscopically were discharged on day 2 (17 patients) or day 3 (nine), median stay was 2.5 days (*Fig. 2*). The reasons for staying in hospital beyond the scheduled 2 days included complications (*Table 4*), difficulty in re-establishing the patient's usual home care service (four patients), chronic hip arthritis pain (one) or a non-functioning epidural catheter (two)

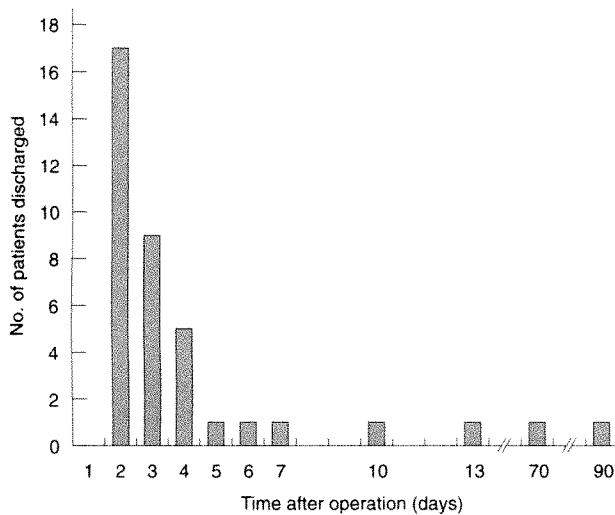


Fig. 2 Day of discharge in 38 elderly patients (median age 81 years) after completed laparoscopic colonic resection. Median stay was 2.5 days

which required treatment with narcotics that resulted in delayed defaecation. Hospital stay of the patients whose operation was converted to an open procedure is shown in *Table 2*.

Complications

Postoperative complications are shown in *Table 4*. Among the patients with complications, two had been discharged on day 2 and 3. One patient was readmitted with signs of small bowel obstruction on day 5 and underwent reoperation on day 9; the other patient was readmitted on day 9 with abdominal pain and had reoperation for anastomotic leakage. No other patients were readmitted. Complications that occurred in the 11 patients whose operation was converted to an open procedure are shown in *Table 2*.

Port-site metastasis

One patient with a Dukes' B tumour in the caecum and invasion into the abdominal wall developed metastases at trocar sites 4 months after operation. One patient with a Dukes' C tumour had widespread intra-abdominal tumour growth including tumour invasion near a trocar site 1 year after operation.

Patient satisfaction

Patients who did not experience major complications were all satisfied with the pain management and the information

given. One patient thought she had been discharged too early (on day 3). With this exception, time of discharge was well accepted and, as described above, also modified individually depending on social factors.

Discussion

Postoperative recovery and hospital stay after colonic resection depends on several factors including the magnitude of surgical trauma, pain, paralytic ileus, fatigue, organ dysfunction as well as use of traditional regimens with gastrointestinal tubes and restriction of oral intake¹⁰. Single-modality intervention with laparoscopically assisted colonic resection has improved recovery and reduced hospital stay after colonic resection from 8–10 to 4–6 days^{1–9}. In previous studies, however, no specific attention has been paid to changes in perioperative protocols required to maximize the advantages of the reduced trauma response obtained by the minimally invasive technique.

In the present study, the laparoscopic approach was combined with a multimodality effort to improve postoperative rehabilitation and reduce hospital stay. Optimal pain relief was ensured by use of epidural local anaesthetics. Early postoperative mobilization and enteral nutrition was enforced. Other factors that may limit early rehabilitation, such as use of gastrointestinal tubes, drains and prolonged bladder catheterization, were avoided. The results of the present study confirm the initial observations in eight patients; such a regimen may significantly enhance postoperative recovery after colonic resection in elderly or high-risk patients and reduce median postoperative hospital stay to 2–3 days in patients with a median age of 81 years¹⁶. It represents a potential major advance compared with previous results^{1–9,17}.

An important finding was that the conventional paralytic ileus period could apparently be reduced to 1–2 days with the combined regimen of laparoscopic surgery, epidural local anaesthetic blockade (without opioids) and early enteral nutrition. Recently Neudecker *et al.*¹⁸ failed to confirm the positive effect of epidural analgesia in laparoscopic sigmoidectomy. However, in that study a low (T9–T12) thoracic epidural analgesia was used, which may explain the side-effects with motor blockade and the insignificant effect on paralytic ileus. Furthermore, the postoperative care protocol was not modified to the same extent as in the present study.

The lack of significant cardiopulmonary complications after completed laparoscopic operations suggests that the multimodal regimen with optimal pain relief, early mobilization and reduced surgical trauma response may reduce postoperative organ dysfunction in these elderly patients.

The surgical complications (anastomotic leakage, mechanical bowel obstruction) seem not to be influenced by the multimodal regimen applied. The institution of early enteral nutrition has been demonstrated to be safe in several randomized controlled clinical trials^{10,11,19}.

As noted in previous studies^{1-9,17} intended laparoscopic colonic resection is not always possible and a conversion rate between of 10 and 20 per cent is often reported. In this study, the majority of patients had malignant disease, and the main cause for conversion was tumour growth into neighbouring organs. Patients whose operation was converted received standard postoperative therapy after open surgery, which included epidural analgesia (containing morphine) and did not include the other elements of the multimodal regimen. Registration of gastrointestinal function, mobilization, pain and fatigue was not performed in these patients as there was no intention of comparing these two groups.

The potential economic benefit of laparoscopic colonic resection is controversial^{1-9,19,20}, mostly because no major reduction in hospital stay has been achieved and because the overall costs in patients with operations converted to open resection have been high^{20,21}. An economic analysis was not performed in the present study and assessment of potential differences will require studies with similar postoperative care protocols for laparoscopically completed, converted and open procedures.

Previous randomized studies comparing hospital stay and morbidity in laparoscopic *versus* open colonic resection have not demonstrated substantial advantages for the laparoscopic technique²⁻⁶. However, revision of perioperative care protocols and introduction of multimodal rehabilitation regimens are important for improving outcome^{10,11}, and there is therefore a need to reconsider the design of future randomized trials designed to compare the two types of surgical technique. In this context it is important to emphasize that preliminary observations have demonstrated that the use of multimodal rehabilitation protocols, similar to those used in the present study, have enhanced recovery and reduced hospital stay to between 2 and 5 days after open colonic resection¹²⁻¹⁵. These findings should be taken into consideration in future randomized trials comparing laparoscopic and open colonic resection.

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Results of surgical treatment for faecal incontinence

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Background: This prospective study was designed to evaluate the results of anterior levatorplasty and sphincteroplasty for faecal incontinence with respect to symptomatic and physiological outcome.

Methods: Thirty-one patients with idiopathic (neurogenic) faecal incontinence underwent anterior levatorplasty and 20 patients with traumatic anal sphincter injury underwent anal sphincteroplasty. The outcome of repair was evaluated at 3 and 12 months using a validated questionnaire and anorectal manometry/manovolumetry.

Results: Eighteen of 31 patients in the levatorplasty group reported continence to solid and liquid stools 1 year after operation compared with two patients before surgery ($P < 0.01$). The corresponding figures in the sphincteroplasty group were ten and two of 20 respectively ($P < 0.05$). The incontinence score was improved in both groups after 1 year, from a median score of 14 to 3 in the levatorplasty group ($P < 0.001$) and from 8.5 to 3.5 in the sphincteroplasty group ($P < 0.01$). Improvements in the degree of social and physical handicap were also observed in both groups. No changes were seen in anal canal pressures or rectal sensation in either group.

Conclusion: Despite different aetiologies and surgical approaches, anterior levatorplasty and sphincteroplasty yielded similarly successful results in patients with faecal incontinence. Although a marked symptomatic improvement was seen in both groups, no associated physiological alterations could be detected. The reason for the improvement is thus unclear, but it may result from a stenosing effect in the anal canal.

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Introduction

Faecal incontinence is a complex and challenging surgical problem of diverse aetiology. An incomplete understanding of faecal incontinence is reflected by the existence of multiple surgical approaches with varying results. Anatomical repair of a disrupted anal sphincter without nerve damage is reported to be successful in 70–90 per cent of patients^{1,2}. In cases with evidence of nerve damage, results have been less encouraging^{1,3}. Incontinence of idiopathic (neurogenic) origin is more difficult to deal with because, without a sphincter defect, it is not obvious what approach to choose. As a consequence of the relatively poor results of postanal repair^{4,5} and the observation of a rectocele in a large proportion of patients with idiopathic (neurogenic) faecal incontinence, an anterior rather than a posterior levatorplasty has been investigated. The presence of a deficient perineal body in women with postobstetric neurogenic incontinence has been a further factor in this move, together with the possibility of directly inspecting the

external anal sphincter (EAS) in the anterior hemircumference to verify the results of endoanal ultrasonography.

The primary aim of this prospective study was to evaluate the symptomatic outcome and changes in physiological parameters after sphincteroplasty and anterior levatorplasty. A secondary aim was to search for variables that might be associated with a successful outcome.

Patients and methods

All patients with primary faecal incontinence were initially treated conservatively with bulking agents for a period of at least 2 months and those with persistent incontinence after this period were offered a standardized assessment (see below). After this assessment, the policy was to divide patients into different treatment groups on the basis of clinical and physiological findings. Those with a well defined traumatic sphincter injury (usually secondary to obstetric trauma), i.e. a defect in the EAS visible on ultrasonography, were offered sphincteroplasty and those

Table 1 Pretreatment characteristics in patients treated with anterior levatorplasty or sphincteroplasty

	Anterior levatorplasty (n=31)	Sphincteroplasty (n=20)	P
Age (years)*	68 (40–83)	47 (30–69)	<0.001†
Parity*	3 (1–8)	3 (1–5)	n.s.‡
Prolonged PNTML (>2.5 ms)			
Unilateral	9 of 31	4 of 20	n.s.‡
Bilateral	5 of 31	5 of 20	n.s.‡
Increased fibre density (>1.7)			
Unilateral	4 of 21	1 of 10	n.s.‡
Bilateral	16 of 21	7 of 10	n.s.‡

*Values are median (range). PNTML, pudendal nerve terminal motor latency; n.s., not significant. †Mann-Whitney *U* test, ‡ χ^2 test

with incontinence of idiopathic (neurogenic) origin were offered anterior levatorplasty (postanal repair in men). Patients with a clinically verified rectal prolapse, or an intra-anal intussusception on defaecography, were treated with an abdominal or perineal operation (suture rectopexy, Delorme's operation or Altemeier's procedure).

A prospective study was performed on patients who underwent operative procedures for faecal incontinence between September 1992 and December 1997. A total of 55 patients was studied, none of whom had previously undergone surgery for faecal incontinence. There were four men in the study, but they were excluded because of the small number. Fifty-one women were therefore evaluated. Thirty-one underwent anterior levatorplasty and 20 had anterior sphincteroplasty. Clinical details are given in *Table 1*.

Clinical and physiological assessment

A detailed history complemented by a bowel questionnaire⁶ was obtained from each patient. The degree of incontinence was assessed and graded according to Miller's incontinence scoring system (0, total continence; 18, maximum incontinence)⁷. Three patients had previously undergone haemorrhoidectomy. Five patients had undergone anal sphincter repair immediately following delivery because of a recognized obstetric sphincter tear (grade III–IV). No patient had previous anorectal radiation therapy, and none was suffering from inflammatory bowel disease, anorectal cancer or neurological disease. Digital examination of the anorectum with careful palpation of the EAS during rest and squeeze, and rectoscopy was performed routinely. All patients underwent anorectal manometry⁸ and manovolumetry^{9,10}. Anal canal resting pressure, squeeze pressure,

maximum resting pressure, maximum squeeze pressure and the length of the high-pressure zone were determined. Neurophysiological evaluation (pudendal nerve terminal motor latency (PNTML) and fibre density) was performed as described previously^{11–13}. In addition, all patients were examined with defaecography and anal ultrasonography.

Twenty patients had a sphincter injury (all had a history of at least one complicated delivery), i.e. an anterior defect in the EAS visible on ultrasonography (median size of defect 120° (range 60–180°), median incontinence score 8.5). These patients underwent anal sphincteroplasty. In the remaining 31 patients (median incontinence score 14) an isolated neuropathy or no abnormality at all was observed; these were judged as idiopathic (neurogenic) and treated with anterior levatorplasty (*Table 1*).

Anal ultrasonography and defaecography

The patients were examined in the left lateral position with a Brüel and Kjaer instrument (Diagnostic Ultrasound System 3535; Brüel and Kjaer, Gentofte, Denmark) connected to an endoprobe with a 10-MHz rotating transducer. The rectal endoprobe was contained in a hard conical plastic head filled with degassed water to minimize distortion of the anal canal. The upper, mid and lower anal canal was imaged in all patients. Disruption of the mixed echogenic texture of the EAS was regarded as a criterion of sphincter injury (*Fig. 1*).

Defaecography was performed as described previously¹⁴. Circumferential intussusception was graded into four groups: 6 mm or less, more than 6 mm but not reaching the anal canal (intrarectal), intra-anal and external prolapse.

Operative technique

The surgical procedure was performed in the jack-knife position after the patient had been given prophylactic antibiotics and full mechanical bowel preparation.

Sphincteroplasty

Overlapping sphincteroplasty was performed with four interrupted absorbable sutures and the wounds were closed in a Y fashion, leaving the central portion open for drainage; no stomas were used.

Anterior levatorplasty

The levator ani muscles were approximated in the midline using two layers of 0/0 unabsorbable sutures. The EAS was mobilized and plicated with 4 to 6 absorbable sutures.

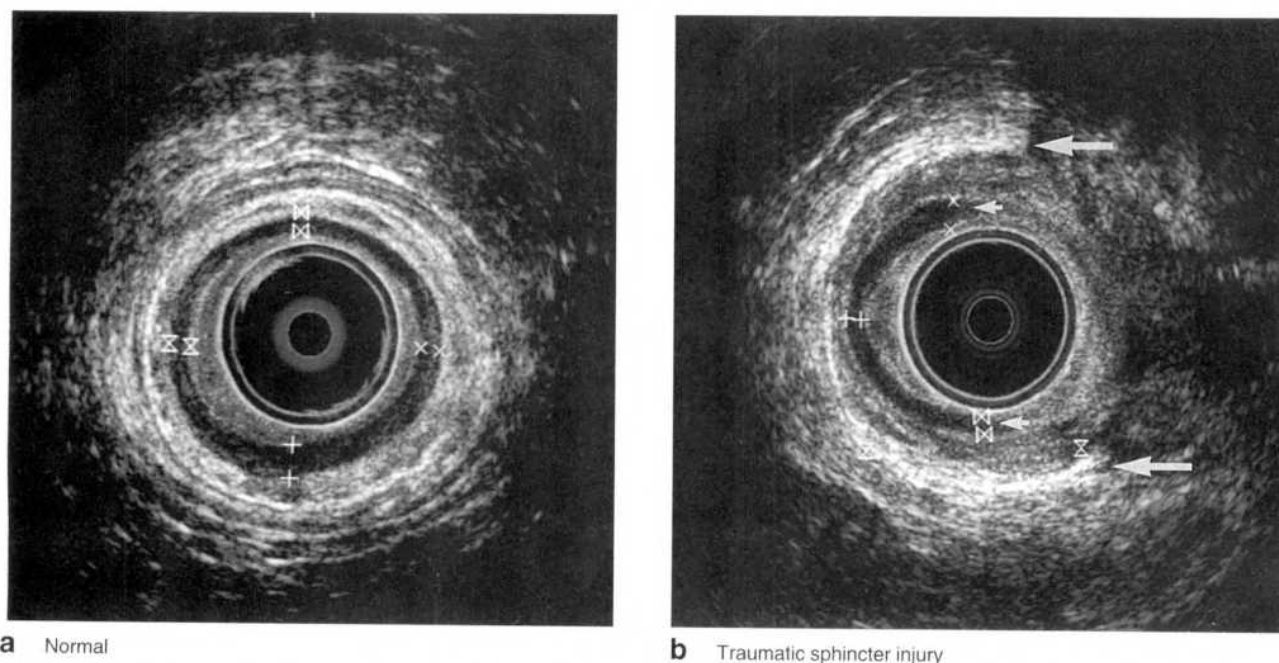


Fig. 1 Anal endosonography showing **a** a normal subject with intact and clearly visible internal (hypoechoic) and external (hyperechoic) sphincter rings and **b** a patient with traumatic rupture, a complete anterior (to the right) division of the external anal sphincter (large arrows) and internal anal sphincter (small arrows)

Follow-up

All patients completed the bowel function questionnaire before, and 3 and 12 months after operation. Anorectal manometry/manovolumetry was also performed in all patients at these intervals.

Definitions

Faecal incontinence *per se* was defined as incontinence to solid or liquid stool. The outcome was considered successful when the patient was continent to solid and loose stools after operation. In the four patients who were incontinent to gas only before operation, a successful outcome was defined as a clear symptomatic improvement, i.e. a reduction in urgency and incontinence episodes for gas.

Statistical analysis

Paired comparisons of proportions were performed with McNemar's test and of numerical values with the Wilcoxon signed rank test. Correlations were assessed by Spearman's rank test. Comparisons between groups were performed using Mann-Whitney *U* test and χ^2 test was used to compare proportions. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Clinical results

The median hospital stay after anterior levatorplasty and sphincteroplasty was 4 days (range 2–10 and 3–8 days respectively). Two patients had a postoperative wound infection after anterior levatorplasty, which was treated successfully with drainage and antibiotics. In all patients in whom a sphincter defect was seen on ultrasonography, perioperative macroscopic verification was obtained. Improved incontinence scores were seen at 1-year follow-up in 27 of 31 patients after levatorplasty and in 18 of 20 after sphincteroplasty (Fig. 2). The median incontinence scores were significantly reduced in both groups after 1 year ($P < 0.001$ and $P < 0.01$ respectively). Deterioration was seen in two patients after sphincteroplasty who had higher scores than before operation. Incontinence was improved in both groups and the use of pads was reduced, although this was most pronounced after levatorplasty (Table 2). Improvements in terms both of social and physical handicap and of deferring time were seen in both groups. The percentage of toilet time spent straining was 11 per cent before treatment, compared with 17 per cent after 3 months and 16 per cent after 12 months in the levatorplasty group.

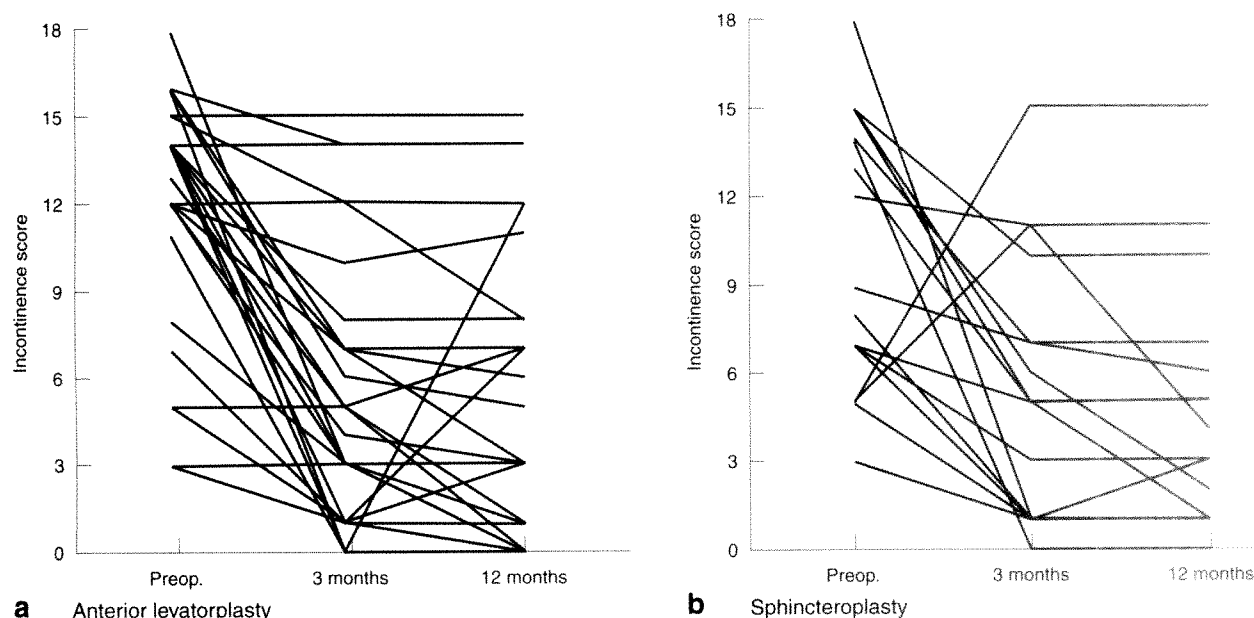


Fig. 2 Postoperative changes in incontinence score after **a** anterior levatorplasty ($n = 31$) and **b** sphincteroplasty ($n = 20$)

Table 2 Clinical results after anterior levatorplasty and sphincteroplasty

	Anterior levatorplasty ($n = 31$)			Sphincteroplasty ($n = 20$)		
	Preop.	3 months	12 months	Preop.	3 months	12 months
Incontinence <i>per se</i>	29	15¶	13¶	18	11§	10§
Incontinence score*	14 (3–18)	3 (0–15)¶	3 (0–15)¶	8.5 (3–18)	5 (0–15)§	3.5 (0–15)§
Use of pads	25	13¶	10¶	10	8	4‡
Impact on lifestyle						
Social handicap	25	12¶	12¶	18	5¶	5¶
Physical handicap	28	14¶	12¶	20	10¶	7¶
Percentage straining (%)*†	11 (0–67)	17 (0–68)	16 (0–71)	13 (0–51)	18 (0–54)	19 (0–69)
Deferring time*†						
Loose stool	12 (0–55)	13 (0–28)	22 (0–38)‡	5 (0–23)	12 (0–35)‡	24 (10–36)¶
Solid stool	23 (0–67)	35 (0–110)§	53 (0–110)¶	15 (0–100)	39 (0–85)‡	45 (0–100)§

*Values are median (range). Incontinence score ranged from 0 to 18.†Visual analogue scale (arbitrary units; percentage straining: 10 mm = 10 per cent; deferring time: 10 mm = 1 min). ‡ $P < 0.05$, § $P < 0.01$, ¶ $P < 0.001$ (McNemar test for categorical paired comparisons; Wilcoxon signed rank test for numerical paired comparisons)

The corresponding figures were 13, 18 and 19 per cent in the sphincteroplasty group.

Physiological results

The squeeze pressure was improved in the sphincteroplasty group after 12 months ($P < 0.05$), whereas the maximum squeeze pressure was improved in the anterior levatorplasty group ($P < 0.05$) (Table 3). The high-pressure zone and the threshold for eliciting the rectoanal inhibitory reflex were unchanged by the operation in both groups. There were no significant changes in the longitudinal high-pressure zone

profile during rest and squeeze (Fig. 3). No manometric variable was associated with outcome in either group (data not shown).

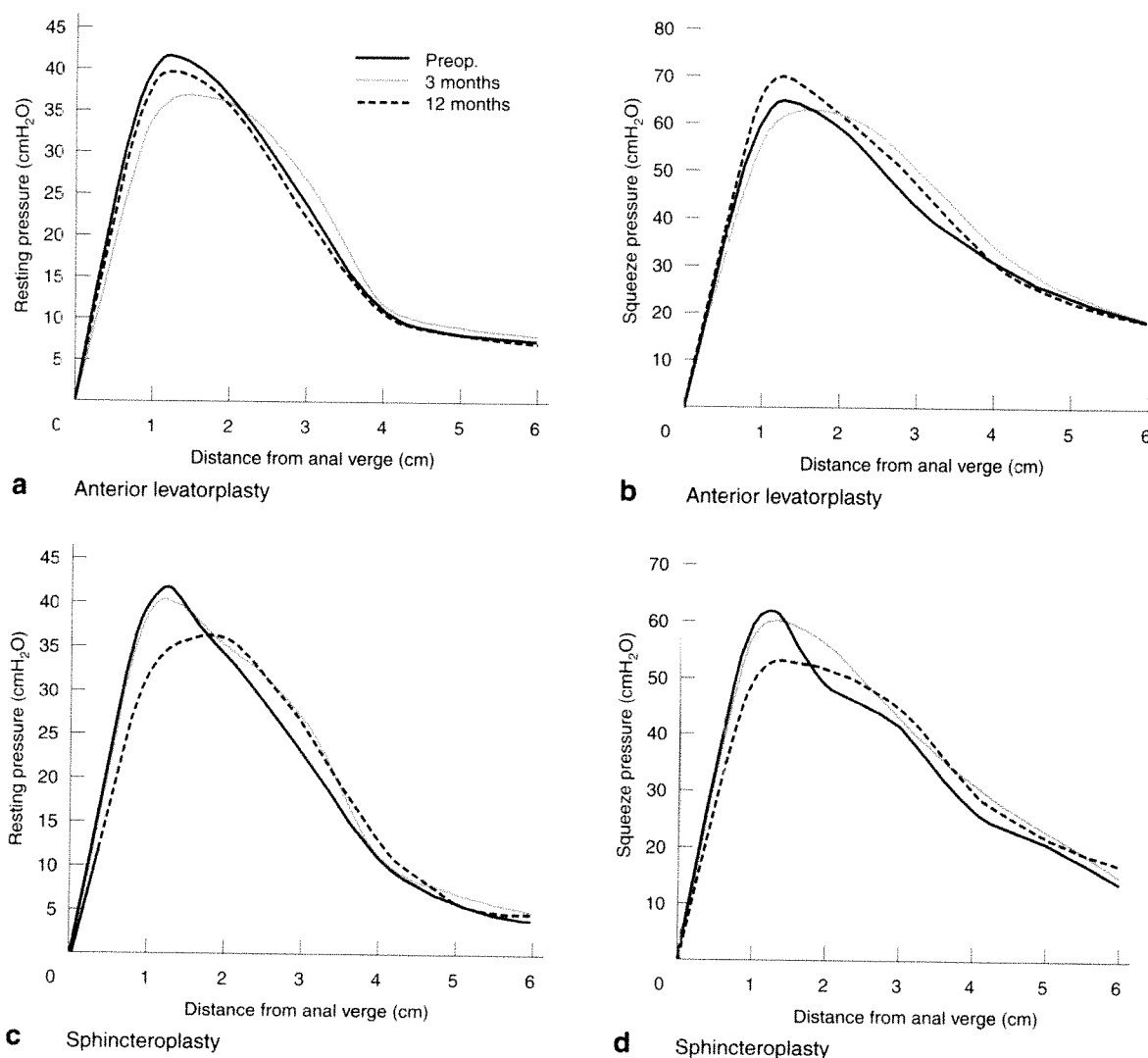
Discussion

Faecal incontinence affects up to 5 per cent of the normal population¹⁵, with higher figures for elderly and institutionalized subjects¹⁶. The aetiology of faecal incontinence is multifactorial, but some well defined causes have been identified.

Table 3 Results of surgery for sphincteroplasty and anterior levatorplasty as defined by physiological and clinical variables

	Anterior levatorplasty (n=31)			Sphincteroplasty (n=20)		
	Preop.	3 months	12 months	Preop.	3 months	12 months
Resting pressure (cmH ₂ O)*	40 (13–88)	42 (14–98)	40 (14–88)	34 (22–98)	36 (20–90)	39 (26–85)
Squeeze pressure (cmH ₂ O)*	85 (33–190)	88 (31–185)	82 (31–220)	72 (46–134)	80 (40–153)	85 (46–135)‡
MRP (cmH ₂ O)†	42 (12–79)	43 (10–66)	42 (16–73)	37 (15–103)	41 (9–123)	40 (8–118)
MSP (cmH ₂ O)†	63 (36–108)	61 (32–129)	64 (33–132)‡	58 (23–135)	66 (5–136)	65 (5–138)
High-pressure zone (cm)	3 (1–5)	3 (1–5)	3 (1–5)	3 (1–5)	3 (2–5)	3 (1–4)
RAIR (cmH ₂ O)	15 (5–25)	15 (5–35)	15 (5–25)	15 (10–40)	15 (10–25)	15 (10–35)
Rectal compliance (ml per 40 cmH ₂ O)	165 (76–285)	176 (89–304)	158 (68–274)	163 (85–250)	140 (93–257)	154 (91–231)

Values are median (range). *Anorectal manovolumetry, †station pull-through manometry. MRP, maximum resting pressure; MSP, maximum squeeze pressure; RAIR, rectoanal inhibitory reflex. ‡ $P < 0.05$ (Wilcoxon signed rank test)

**Fig. 3** Longitudinal pressure profile at rest and squeeze before and after anterior levatorplasty (a and b) and sphincteroplasty (c and d)

Vaginal delivery is complicated by a significant sphincter injury in 0.5–2.5 per cent of cases¹⁷. About 3 years after primary suture, up to 50 per cent of the women complain of continence disturbance¹⁷. The incidence of faecal incontinence due to obstetric sphincter injury in Sweden is approximately 750 cases per year¹⁸.

Another distinct cause of faecal incontinence is rectal prolapse or intra-anal intussusception¹⁹. The pathophysiological mechanism in this group is probably a combination of stretch injury to the pudendal nerve and repetitive dilatation of the sphincters eventually resulting in a patulous anus. Furthermore, the intussusception may cause a sustained reflex inhibition of the internal anal sphincter²⁰.

Postobstetric faecal incontinence may also be due to a stretch injury of the pudendal nerve²¹. The risk of this complication is probably increased when there is a prolonged second stage of labour or when instrumental extraction is necessary. Another cause of stretch injury of the pudendal nerve may be forceful and prolonged straining²². This mechanism may thus be relevant in patients with severe constipation, and the hypothesis is further supported by the clinical observation that faecal incontinence and constipation frequently coexist. Before the vulnerability of the pudendal nerve to stretch injury was known, these patients were referred to as idiopathic since no anatomical explanation for their symptoms could be found. However, since the introduction of neurophysiological tests such as PNTML and fibre density in the investigation of faecal incontinence, patients with objective signs of neuropathy are commonly referred to as neurogenic. To avoid misunderstanding, in the present study these patients were labelled as idiopathic (neurogenic).

A number of surgical techniques are currently being used for the correction of faecal incontinence. This may indicate that an ideal treatment for this disabling state does not exist. The clinical outcome for traumatic sphincter injury in this study was fairly good, with a success rate of 50 per cent (ten of 20 continent to solid and liquid stools after 12 months), although a larger proportion of the patients had a reduction in incontinence score. Previous studies have reported a somewhat higher success rate, but the definition of success varies and can make comparisons difficult^{1,2}. Using an anterior approach in the idiopathic (neurogenic) group a satisfactory outcome was also achieved, with 18 of the 31 patients being continent to solid and liquid stool after 12 months.

The traditional view is that idiopathic (neurogenic) faecal incontinence is associated with a poor prognosis after surgical treatment, especially after long-term follow-up^{23,24}. In contrast, patients with an isolated sphincter injury are believed to have a good prognosis after sphincteroplasty, provided that there is no concomitant

nerve damage³. However, the present results do not really support this view since results were almost identical 1 year after surgery, irrespective of the origin of incontinence. Patients with neurogenic incontinence actually improved to the same extent as those with a sphincter injury. In view of the low morbidity and the negligible surgical trauma, the authors believe that patients with neurogenic incontinence should not be denied surgery, provided that conservative treatment has been attempted and they have been evaluated carefully. In view of the lack of correlation between PNTML/fibre density and outcome, the routine use of neurophysiological evaluation in these patients may be questioned. Depending on the skill of the clinical examiner, the use of anal pressure measurements and defaecography may also be superfluous. Further studies of this population are needed to evaluate the long-term results since previous studies have shown that symptoms sometimes recur^{23,24}.

Few studies have evaluated the outcome after anterior levatorplasty, and the present results are comparable to those of previous studies^{25,26}. It is not known, however, whether anterior levatorplasty is superior to postanal repair in the long term.

Despite the marked symptomatic improvement in both groups in the present study, no associated physiological alterations could be identified. There was a tendency towards increased squeeze pressure in both groups, but the improvement cannot be attributed to the very moderate increment recorded. Nor were any changes in resting pressure, longitudinal pressure profile, rectal compliance or rectal sensory threshold observed.

What is the explanation for the symptomatic improvement? A placebo effect cannot be ruled out entirely, although it appears unlikely that patients would stop using pads without a real improvement in continence. Furthermore, several symptoms found to be reproducible in the validation of the bowel questionnaire⁶ (incontinence *per se*, deferring time, physical and social handicap) were clearly improved after surgery. A possible explanation for the improvement is a stenosing effect of surgery in the anal canal, i.e. a 'biological' Thiersch effect, causing increased resistance to flow through the anus which may not have been detected in the pressure measurements. This is supported by the slight postoperative increase in straining effort reported by the patients.

In conclusion, anterior levatorplasty and sphincteroplasty yielded a successful result in approximately every second patient suffering from either idiopathic faecal incontinence or sphincter injury. No obvious objective indices were found at follow-up to explain this improvement. One possible hypothesis may be that in both procedures a stenosing effect is created simply by the fact that the pelvic floor is repaired (approximated in the

midline) and the EAS plicated or sutured with an overlapping repair.

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Effects of the combination of blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer

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Background: The frequency of postoperative infectious complications is significantly increased in patients with colorectal cancer receiving perioperative blood transfusion. It is still debated, however, whether perioperative blood transfusion alters the incidence of disease recurrence or otherwise affects the prognosis.

Methods: Patient risk variables, variables related to operation technique, blood transfusion and the development of infectious complications were recorded prospectively in 740 patients undergoing elective resection for primary colorectal cancer. Endpoints were overall survival ($n = 740$) and time to diagnosis of recurrent disease in the subgroup of patients operated on with curative intention ($n = 532$). The patients were analysed in four groups divided with respect to administration or not of perioperative blood transfusion and development or non-development of postoperative infectious complications.

Results: Overall, 19 per cent of 288 non-transfused and 31 per cent of 452 transfused patients developed postoperative infectious complications ($P < 0.001$). The median observation period was 6.8 (range 5.4–7.9) years. In a multivariate analysis, risk of death was significantly increased among patients developing infection after transfusion ($n = 142$) compared with patients receiving neither blood transfusion nor developing infection ($n = 234$): hazard ratio 1.38 (95 per cent confidence interval (c.i.) 1.05–1.81). Overall survival of patients receiving blood transfusion without subsequent infection ($n = 310$) and patients developing infection without preceding transfusion ($n = 54$) was not significantly decreased. In an analysis of disease recurrence the combination of blood transfusion and subsequent development of infection (hazard ratio 1.79 (95 per cent c.i. 1.13–2.82)), localization of cancer in the rectum and Dukes classification were independent risk factors.

Conclusion: Blood transfusion *per se* may not be a risk factor for poor prognosis after colorectal cancer surgery. However, the combination of perioperative blood transfusion and subsequent development of postoperative infectious complications may be associated with a poor prognosis.

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Introduction

Perioperative transfusion with allogeneic blood components is suggested to increase the risk of infectious complications after surgery for intra-abdominal disease¹. Blood transfusion-induced impairment of the immune response may reduce resistance to bacterial infection as observed in patients with postoperative infectious complications². The impaired immune response following blood transfusion has also been suggested to play a role in

resistance to tumour growth³. It is still debated, however, whether perioperative blood transfusion *per se* has a causal relationship to the development of recurrent disease and reduced survival of patients undergoing macroscopically curative surgery for colorectal cancer⁴. Reports from retrospective⁵ and prospective^{6,7} studies of patients with colorectal cancer indicate a causal relationship. It is more difficult to demonstrate this relationship in studies of patients with various other solid malignant tumours^{8–12}. Therefore, it has been suggested that other important risk

factors may confound translation of results from studies of the relation between perioperative blood transfusion and poor prognosis in cancer surgery¹³, and a consensus has still not been achieved.

The development of postoperative bacterial infection depends on various risk factors. Differences in frequency of postoperative infectious complications between patients with cancer with a high risk of bacterial contamination, such as those undergoing alimentary tract surgery^{5-7,11,12}, and patients with a low risk, such as those undergoing breast, cervix and head and neck surgery⁸⁻¹⁰, suggest a certain role for bacterial contamination. Postoperative bacterial infectious complications may possibly play an additional role to the effect of perioperative blood transfusion on survival and recurrence after operations for various malignant diseases. The purpose of the present study was to evaluate the effect of perioperative blood transfusion and postoperative infectious complications on prognosis after surgery for colorectal cancer.

Patients and methods

Study population

Seven hundred and forty men and women scheduled for elective surgery of biopsy-verified primary colorectal adenocarcinoma were included in this prospective, clinically controlled study performed in 20 Danish centres of the RANX05 Colorectal Cancer Study Group. The study was designed primarily to compare the effect of the histamine-2 receptor antagonist ranitidine *versus* placebo on long-term survival. As previously described, ranitidine treatment had no effect on the development of infectious complications¹⁴ or overall survival¹⁵, and therefore stratification for treatment was not performed. All patients were without clinical signs of infectious disease, and none had been treated with systemic steroids, antibiotics, antiviral drugs or cytotoxic agents within 2 weeks before entry into the study. Patients with severe concurrent illness, such as leukaemia or human immunodeficiency virus infection, and patients undergoing chemotherapy, radiotherapy and/or other adjuvant therapy for cancer or expected to undergo such therapies within the study period were not included.

All patients were prepared for the operation, by bowel evacuation and anticoagulant therapy, according to standard procedures. All received preoperative antibiotic prophylaxis with metronidazole 1.5 g and cefuroxime 3 g intravenously. No other antibiotic treatment was given after operation, unless specifically required for postoperative infectious complications. All surgical procedures were performed from April 1991 to August 1993 before total mesorectal excision was introduced in Denmark.

Blood components

Perioperative transfusion was defined as transfusion of buffy coat-depleted red cells suspended in saline, adenine, glucose and mannitol (SAGM blood) and/or fresh frozen plasma from 30 days before until 14 days after surgery. In case of an infectious complication the transfused units were recorded only until occurrence of the infection. Units given after diagnosis of an infectious complication and/or in connection with relaparotomy were not included to avoid the effect of blood transfusion biasing the single effect of an infectious complication. SAGM blood and plasma were prepared according to standard procedures of the participating institutions. The red cells were stored at +4°C for a maximum of 35 days. Fresh frozen plasma was stored at -25°C for a maximum of 6 months. Transfusion of platelet components was performed in only three patients, who also received SAGM blood.

Indications for blood transfusion were not established and transfusion was given following clinical decisions of surgeons and/or anaesthesiologists.

Endpoints

Patients were assessed daily during the hospitalization period and a clinical examination was performed on the day of discharge. Finally, all patients were examined in the outpatient clinic or in the surgical ward when still not discharged, 30 days after primary surgery.

Wound infection, including perineal infection in patients who underwent abdominoperineal resection of the rectum, was defined as the presence of pus, either discharged spontaneously or requiring drainage. Intra-abdominal abscess was verified by either surgical drainage or by ultrasonographically guided aspiration of pus. Anastomotic leakage was defined as radiologically verified fistula to bowel anastomosis or diagnosed by relaparotomy. Pneumonia was defined by fever above 38.5°C and a positive radiograph, and requiring antibiotic treatment. Septicaemia was defined as clinical symptoms with a positive blood culture. Non-symptomatic or minor urinary tract infection was not recorded, and therefore only included if complicated by septicaemia.

Patients were examined in the outpatient clinic every 3 months for up to 5 years and thereafter when required. Anastomoses within reach of a rectoscope were examined every 3 months for the first year and thereafter at least once annually. If a patient had any complaints, a search for disease recurrence was initiated. Local recurrence of disease was verified by biopsies collected during colonoscopy/rectoscopy. Distant metastases were verified by ultrasonography, computed tomography or bone scan and supplemented with

fine-needle biopsy if reoperation was indicated. Metastases located in the mesentery with primary tumours of the colon and pelvic metastases with primary tumours of the rectum were classified as local recurrence. Overall survival (or death from all causes) was followed by using the central personal registration (identity card) number in the Danish central national registry. The expected mortality rate from all causes was calculated in a cohort with the same age and sex distribution as the patients studied, using the vital statistics for the Danish population.

Statistical analysis

The SPSS software package (SPSS, Chicago, Illinois, USA) was used to manage patient data and to perform statistical calculations. Continuous variables were categorized using the median or tertiles as cut-off points. Tests of independence were done using the χ^2 or Fisher's exact test. Rank statistics were used to calculate correlation coefficients (Spearman rank correlation) and to test hypotheses on location (Mann-Whitney test). The Kaplan-Meier method was used to estimate survival probabilities, and the log rank test was used to test for equality of strata. Logistic regression analysis and the Cox proportional hazard model were applied for multivariate analysis. The significance level was set at 5 per cent.

Results

The median observation time was 6.8 (range 5.4–7.9) years and no patient was lost to follow-up. In total 452 patients received a median of 3 units of SAGM blood and/or fresh frozen plasma (397 patients received SAGM blood, 53 patients received both SAGM blood and fresh frozen plasma, and two patients received fresh frozen plasma only). The surgical procedures included 13 laparotomies without resection, 137 right hemicolectomies, 18 transverse resections, 33 left hemicolectomies, 145 sigmoid resections, 177 low anterior resections, 113 abdominoperineal resections, 59 Hartmann's procedures, 15 colostomies without resection and 30 other surgical procedures (subtotal colectomies inclusive). The transfusion rate varied from 41 to 83 per cent between the 20 centres ($P=0.09$). It was highly dependent, however, on the surgical procedures performed, mainly owing to higher rates in procedures involving rectal resection. The transfusion rate was 74 per cent in procedures with rectal and 51 per cent with non-rectal cancer localization. The rate of primary anastomosis was 86 per cent in non-transfused and 87 per cent in transfused patients.

Infectious complications developed in 196 patients; of these 55 had more than one infection. The distribution of

Table 1 Postoperative infectious complications in 740 patients with colorectal adenocarcinoma

	Not transfused (<i>n</i> =288)	Transfused (<i>n</i> =452)	<i>P</i>
Infectious complications			
Anastomotic leakage	14 (5)	31 (7)	0.3
Intra-abdominal abscess	11 (4)	19 (4)	0.8
Septicaemia	3 (1)	23 (5)	0.004
Wound/perineal infection	15 (5)	55 (12)	0.002
Pneumonia	28 (10)	74 (16)	0.01
Overall	54 (19)	142 (31)	0.000

Values in parentheses are percentages

the infectious complications is shown in Table 1. Development of intra-abdominal abscess and anastomotic leakage were as isolated events independent of blood transfusion. Overall, when corrected for double infections, the patients who received blood transfusion had a significantly higher frequency of infectious complications than non-transfused patients ($P<0.001$). Other potential risk factors for development of infectious complications are shown in Table 2, which shows that Dukes stage and operating surgeon had no significant influence. Prolonged operation time was a risk factor in univariate analysis, but was highly dependent on the tumour localization and therefore lost significance in a multivariate analysis with separation of colonic and rectal tumours. Increasing weight and blood loss, rectal tumour involvement and blood transfusion, although marginal, were independent risk factors for the development of infectious complications.

Using univariate analysis, blood transfusion was associated with decreased survival: hazard ratio 1.32 (95 per cent confidence interval (c.i.) 1.09–1.59). There was no significantly increased risk between patients ($n=211$) receiving 4 units or more compared with patients ($n=241$) receiving 3 units or less (hazard ratio 1.24 (95 per cent c.i. 0.99–1.55)). The patients were divided into four groups: patients who did not receive blood transfusion and did not develop infectious complications ($n=234$), patients who received blood transfusion but did not develop infectious complications ($n=310$), patients who did not receive blood transfusion until development of any infectious complication ($n=54$) and patients who received blood transfusion and subsequently developed an infectious complication ($n=142$). The median amount transfused was 3 (range 1–40) units in patients who received blood transfusion and subsequently developed an infectious complication, which was not significantly different from the 3 (1–45) units in patients who received blood transfusion but did not develop infectious complications ($P=0.49$). A significant difference

Table 2 Potential risk factors associated with development of postoperative infectious complications in 740 patients

	Total	Infected*	P (univariate)	Relative risk†
Patient weight (kg)				
< 63	247	47 (19)	0.001	1
63–75	261	70 (27)		1.50 (0.97–2.32)
> 75	232	79 (34)		2.00 (1.29–3.09)
Dukes stage				
A	73	16 (22)	0.8	
B	275	72 (26)		
C	223	63 (28)		
D	169	45 (27)		
Tumour localization				
Colon	419	80 (19)	0.000	1
Rectum	321	116 (36)		1.73 (1.18–2.54)
Duration of surgery (min)‡				
< 120	294	65 (22)	0.003	1
120–170	191	44 (23)		0.82 (0.52–1.30)
> 170	254	87 (34)		0.99 (0.64–1.55)
Blood loss (ml)				
< 400	292	50 (17)	0.000	1
400–900	201	51 (25)		1.32 (0.83–2.09)
> 900	247	95 (38)		1.73 (1.05–2.86)
Operating surgeon‡				
Consultant/specialist	511	141 (28)	0.6	
Supervised senior registrar	83	19 (23)		
Senior registrar	122	31 (25)		
Blood transfusion				
No	288	54 (19)	0.000	1
Yes	452	142 (31)		1.50 (1.00–2.24)

Values in parentheses are *percentages or †95 per cent confidence intervals. ‡Owing to missing values, the total numbers are less than 740. The relative risk is based on logistic regression analysis including significant factors from the univariate analysis

in overall survival between the four groups was mainly due to a reduced survival in the patients who received blood transfusion and subsequently developed infectious complications (*Fig. 1*). There were no significant differences between the three other groups.

In a multivariate analysis adjusting for patient age, sex, Dukes classification, rectal/colonic tumour localization and blood loss over/under the median of 550 ml, the hazard ratio of death among the patients who received blood transfusion and subsequently developed infectious complications was 1.38 (95 per cent c.i. 1.05–1.81) compared with non-infected patients who did not receive blood transfusion. The risk was also significantly higher (hazard ratio 1.30 (95 per cent c.i. 1.03–1.66)) than in patients who received blood transfusion without developing infectious complications, but not than in patients who did not receive blood transfusion until development of infectious complications (hazard ratio 1.23 (95 per cent c.i. 0.83–1.83)). Hazard ratios for patients developing infectious complications without preceding blood transfusion and for patients who received blood transfusion without subsequent development of infectious complications were not significantly increased in the multivariate analysis.

Five hundred and forty-eight of the 740 patients were classified as having Dukes A–C disease on histological examination and were operated on with curative intention. Five hundred and thirty-two patients survived for more than a month after the operation. Disease recurrence was detected in 193 of these patients. There was no significant difference in the recurrence rate between the 20 hospitals. Potential risk factors are listed in *Table 3*. The significant factors were tumour localization, Dukes classification, duration of surgery, blood loss and infectious complications. In cases of multiple infections, the first occurring type is listed. Intra-abdominal abscess and septicaemia were rare as a first infection, as these were frequently additive complications to anastomotic leakage and/or pneumonia. In single comparisons with no infection, anastomotic leakage, wound infection and pneumonia were associated with a higher recurrence rate ($P=0.007$, $P=0.04$ and $P=0.02$ respectively). Although blood transfusion compared with no transfusion was associated with a higher recurrence rate ($P=0.03$), no dose dependency discriminating between 3 or less and more than 3 units was observed. The effect of blood transfusion and infectious complications on recurrence is shown in *Fig. 2*. The significant

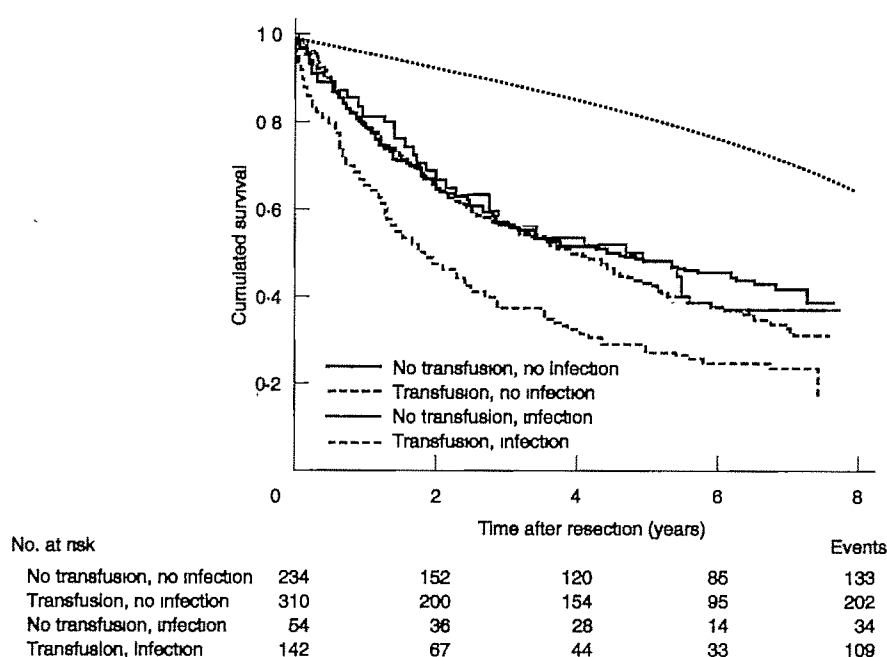


Fig. 1 Kaplan-Meier analysis of overall probability of survival in 740 patients with colorectal cancer. The upper dotted line represents the overall survival in the cohort of all Danish inhabitants with the same age and sex distribution as the study population. $P = 0.0001$ between the four groups (log rank test)

difference between the groups was mainly due to a high recurrence rate among patients who received blood transfusion and subsequently developed infectious complications. In isolated comparisons, the differences in recurrence rates in patients who received blood transfusion without development of infectious complications and patients who did not receive blood transfusion until development of infectious complications compared with the patients who neither received blood transfusion nor developed infectious complications did not reach statistical significance.

After adjustment for the above-mentioned significant risk factors, patients who received blood transfusion and subsequently developed any infectious complication had an independent significantly higher risk of recurrence (*Table 4*). The risk was also significantly higher than that in patients who received blood transfusion without development of infectious complications ($P = 0.03$), but not compared with that in patients who did not receive blood transfusion until development of infectious complications ($P = 0.2$). A tumour localized in the rectum and Dukes stage of disease were the only other significant independent risk factors.

Local recurrence in rectal cancer may be of special interest in these patients undergoing vigorous follow-up every third month. The effect of blood transfusion and infectious complications on local recurrence is shown in

Fig. 3. Receipt of a blood transfusion and development of infectious complications, as separate events, were not significant. However, the combination of development of an infectious complication after blood transfusion was significantly different from the group with none of the two events ($P = 0.002$) and, after correction for Dukes stage, the hazard ratio was 2.84 (95 per cent c.i. 1.36–5.94) for development of local recurrence.

Discussion

The present study confirms that perioperative blood transfusion is associated with an increased risk of infectious complications^{1,2}. This was especially evident for wound infection and pneumonia, but also for overall infection even with correction for blood transfused after onset of the infection. Blood transfusion, in univariate analysis, was also associated with reduced long-term survival in patients undergoing elective operation for primary colorectal cancer^{5–7}. Moreover, by dividing the patient population into four groups it has been demonstrated that patients with perioperative blood transfusion and subsequent development of postoperative infectious complications represent a group with a particularly poor prognosis, independent of Dukes classification. The only additional independent significant prognostic parameter was tumour localization in the rectum. The group of patients receiving blood

Table 3 Possible risk variables and relation to disease recurrence, local or distant ($n = 532$)

	Total	Events	P†
Age (years)			
< 65	176	64 (36)	0.92
65–73	178	66 (37)	
> 73	178	63 (35)	
Sex			
Female	215	77 (36)	0.51
Male	317	116 (37)	
Endocrine disease			
Yes	31	6 (19)	0.13
No	501	187 (37)	
Preoperative P-albumin ($\mu\text{mol/l}$)*			
< 520	172	54 (31)	0.52
520–610	172	61 (35)	
> 610	174	68 (39)	
Weight (kg)			
< 63	172	56 (33)	0.52
63–75	190	71 (37)	
> 75	170	66 (39)	
Tumour localization			
Colon	297	86 (29)	0.000
Rectum	235	107 (46)	
Dukes stage			
A	69	12 (17)	0.000
B	257	68 (26)	
C	206	113 (55)	
Duration of surgery (min)			
< 120	198	66 (33)	0.01
120–170	155	48 (31)	
> 170	179	79 (44)	
Blood loss (ml)			
< 400	200	57 (29)	0.002
400–900	162	61 (38)	
> 900	170	75 (44)	
Blood transfusion (units)			
None	209	68 (33)	0.052
1–3	180	76 (42)	
> 3	143	49 (34)	
Operating surgeon*			
Consultant/specialist	384	150 (39)	0.06
Supervised senior registrar	59	16 (27)	
Senior registrar	89	27 (30)	
Infectious complication (first)			
No	394	132 (34)	0.01
Anastomotic leak	23	13 (57)	
Abscess	6	2 (33)	
Septicaemia	9	1 (11)	
Wound infection	31	15 (48)	
Pneumonia	69	30 (43)	

Values in parentheses are percentages. *Owing to missing values, the total numbers are less than 532. †Log rank test

transfusion without developing serious infections did not have a significantly increased risk of early disease recurrence and/or death. The slightly increased risk associated with blood transfusion and development of an infectious complication as separate events, in particular local recur-

rence in patients with rectal cancers, however, suggests a synergistic effect between infectious complications and the effect of blood transfusion.

There may be certain confounders in evaluating the effect of blood transfusion on survival. In comparison to the Danish background population it is obvious that factors other than blood transfusion and infectious complications are important (*Fig. 1*). However, it is noteworthy that there was no clear transfusion dose–response relation as shown previously⁵ and, most importantly, that the amount of blood transfused was not a predictor for selecting the infected patients among the transfused patients. The influence of sex on survival in the present study probably reflects the overall life expectancy in a representative healthy population¹⁶. Disease recurrence was associated with factors that may be confounders of more advanced disease, i.e. more complicated operations. In univariate analysis, duration of surgery and blood loss were significant risk factors but, as these were highly dependent on tumour localization, both factors lost their significance in multivariate analysis when rectal *versus* colonic localization was included. Although concentration of albumin has been shown to be a prognostic indicator for patients with curable colorectal cancer¹⁷, it had no significant influence on survival in the present study, even in a survival analysis of the 532 patients who underwent curative resection (data not shown). The finding that the combination of blood transfusion and subsequent development of infectious complications was an independent risk factor for both disease recurrence and death suggests that the prognostic effect may be mediated through an impact on residual disease. However, death from postoperative infectious complications did not influence the poor prognosis, as only patients cured by resection and surviving for more than 30 days after operation were included in the recurrence calculations.

Various postoperative infectious complications have been suggested previously to play a role in the survival of patients with cancer. Thus, postoperative septic fever was suggested as a prognostic factor for recurrence of colorectal carcinoma¹⁸, but others could not confirm the suggestion^{19,20}. Anastomotic leakage may be a risk factor for local recurrence of colorectal cancer, but the mechanism is still unknown^{21,22}. Wound infection may be an independent prognostic sign for recurrence after resection of head and neck cancer²³, but the possible additional effect of blood transfusion was not considered.

The mechanism by which blood transfusion may exert its effect on cancer recurrence is largely unknown. It is suggested to be partly similar to mechanisms leading to infectious complications, but because of the coincidence it may be difficult to discriminate between specific mechan-

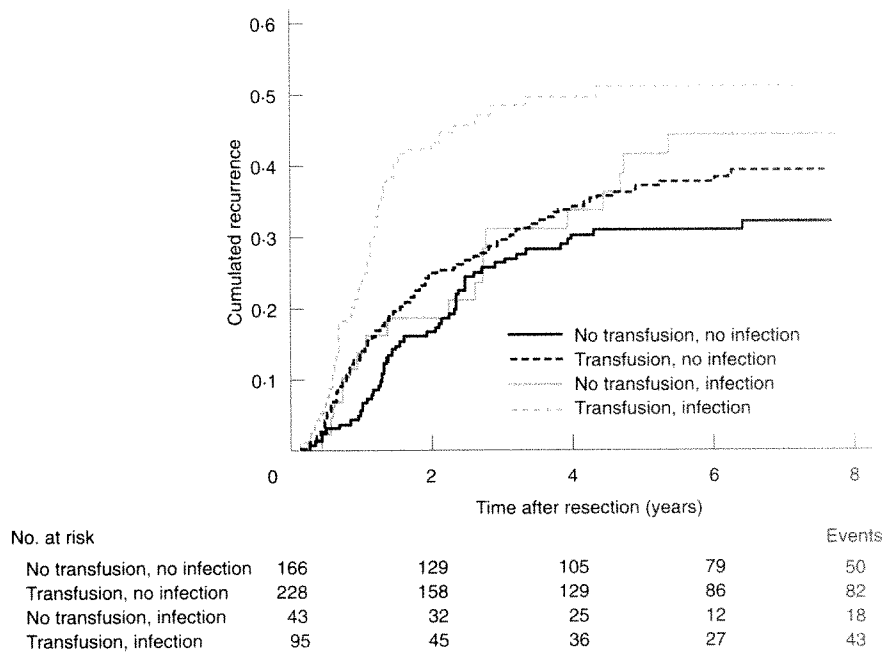


Fig. 2 Kaplan-Meier analysis of cumulated recurrence after resection with curative intention in 532 patients with colorectal cancer. $P = 0.0027$ between the four groups (log rank test)

isms. The immunosuppressive effect of blood transfusion may be evident within 3 days, may weaken during the following month², but can occasionally be detected even years after the transfusion²⁴. Monocyte human leucocyte antigen DR antigen expression, T cell number and release of certain cytokines are depressed for weeks after operations complicated with infections²⁵⁻²⁷, but in these studies no correction for differences in blood transfusion has been considered. The suggestion of a marked depression of immune competence owing to the combination of blood transfusion and infection compared with infection alone has, however, been verified in an animal model²⁸.

In addition to immunomodulation, tumour cell stimulating effects may be considered. Bioactive substances are accumulated extracellularly during storage of blood²⁹, in particular angiogenesis stimulating factors such as vascular endothelial growth factor (VEGF)³⁰. VEGF may be involved in colorectal tumour progression and seems important for wound healing^{31,32}. As prohibited/complicated wound healing and inflammation involves activated granulocytes, a condition of continuing angiogenic stimulation may develop during wound infection³³. Although this may be beneficial for wound healing it may also accelerate growth of cancer cell remnants or micrometastases³⁴, which has been documented even after 'curative' resection^{35,36}. Inconsistent with this is that severe complications are associated with smaller increases in serum VEGF in patients with polytrauma and burn³⁷. However, these patients may,

Table 4 Multivariate analysis of disease recurrence in 532 patients with colorectal cancer resected with curative intention

	Hazard ratio	P
Tumour localization		
Colon	1	
Rectum	1.72 (1.23-2.42)	0.002
Dukes stage		
A	1	
B	2.08 (1.11-3.89)	0.02
C	5.48 (3.00-10.00)	0.000
Duration of surgery (min)		
<115	1	
115-170	0.78 (0.54-1.14)	0.21
>170	0.99 (0.69-1.43)	0.98
Blood loss (ml)		
<400	1	
400-900	0.94 (0.64-1.39)	0.76
>900	1.01 (0.65-1.57)	0.96
Transfusion/infection group		
No transfusion, no infection	1	
Transfusion, no infection	1.16 (0.80-1.68)	0.43
No transfusion, infection	1.21 (0.70-2.09)	0.49
Transfusion, infection	1.79 (1.13-2.82)	0.01

Values in parentheses are 95 per cent confidence intervals

in this context, not be comparable to electively operated patients with cancer, and a full time course of the angiogenic stimulation in these patients needs to be elucidated.

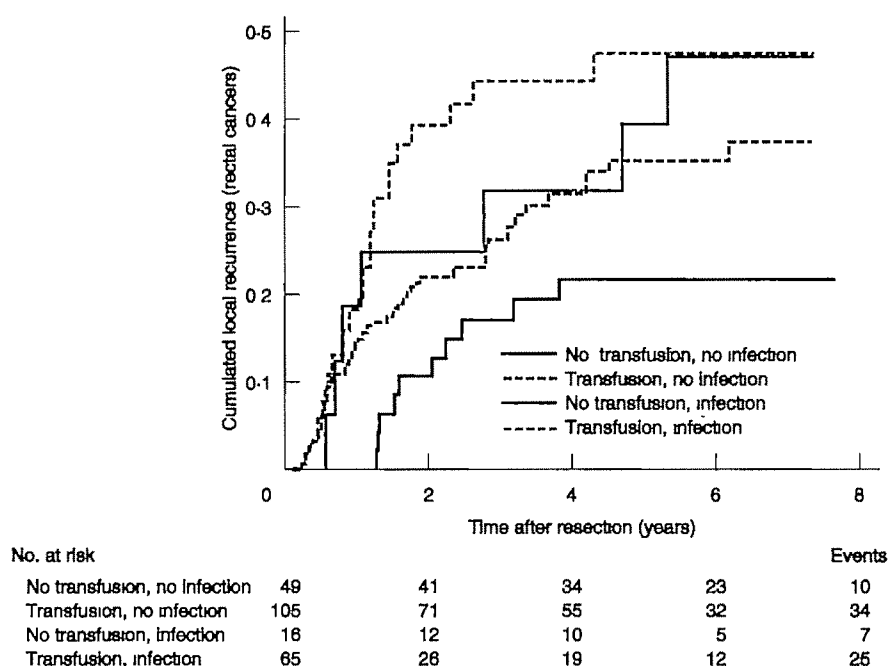


Fig. 3 Kaplan-Meier analysis of cumulated local recurrence after resection with curative intention in 235 patients with rectal cancer. $P = 0.02$ between the four groups (log rank test)

Although both immunological and angiogenic mechanisms may be involved in a concert of cancer cell promoting effects by transfusion and infectious complications, other unknown factors may play an additional role. The present approach to the complex significance of blood transfusion may, however, contribute to another view on the diversity of the effects on prognosis after operation of different cancer types³⁸. It may also be a tool in understanding the diversity in earlier results from studies of patients with colorectal cancer in whom infectious complications were not considered separately, or were even eliminated before statistical evaluation³⁹.

In conclusion, the present results indicate that part of the detrimental effect of blood transfusion on survival and disease recurrence after surgery for colorectal cancer may be exerted through a combination with postoperative infectious complications. The effect is suggested to be due to an extended period of immunosuppression and/or angiogenic stimulation. The observation may partly explain the differences in results from surgical cancer studies with different infection rates and should be taken into consideration in future analysis of results.

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Tacrolimus has less fibrogenic potential than cyclosporin A in a model of renal ischaemia–reperfusion injury

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Background: Cyclosporin is associated with significant chronic nephrotoxicity, manifest in the long term mainly as renal fibrosis. There have been claims that tacrolimus is a less fibrotic drug than cyclosporin, and this study was designed to determine the effect of the two drugs on the expression of fibrosis-associated genes.

Methods: Male Wistar rats underwent clamping of the right renal pedicle for 45 min together with left nephrectomy; this model has previously been shown to be associated with upregulation of fibrosis-associated genes. Experimental groups (six animals per group) received cyclosporin A 10 mg/kg daily, tacrolimus 0.2 mg/kg daily or no treatment. Animals were killed at 16 weeks, and the renal cortical expression of fibrosis-associated genes was studied by means of quantitative reverse transcriptase–polymerase chain reaction.

Results: Tacrolimus-treated animals developed significantly less proteinuria and had lower serum creatinine levels than those receiving cyclosporin. Tacrolimus administration also significantly reduced the expression of transforming growth factor β and tissue inhibitor of metalloproteinases 1, both the products of genes associated with fibrosis. Although cyclosporin treatment reduced levels of the matrix-degrading enzymes, matrix metalloproteinase (MMP) 2 and MMP-9, this was not statistically significant.

Conclusion: Tacrolimus has less nephrotoxicity than cyclosporin in this model. It also appears to have less fibrogenic potential, and this may have implications for the choice of long-term immunosuppressant in renal transplantation.

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Introduction

Chronic allograft nephropathy (CAN) remains a major cause of renal transplant failure¹. It is characterized by progressive functional deterioration, associated histologically with graft fibrosis, and there is no effective therapy at present. Cyclosporin, which is the mainstay of most immunosuppressive regimens in renal transplantation, has no impact on the development of CAN, and it is increasingly appreciated that its nephrotoxicity contributes to the functional and histological deterioration found in this condition. In the past 10 years increasing experience has been gained with the use of tacrolimus, a macrolide that acts to inhibit T-cell proliferation in a similar way to cyclosporin. Tacrolimus is 100 times more potent than cyclosporin, and large clinical trials have confirmed that it reduces the rate of acute rejection^{2,3}. While tacrolimus, like cyclosporin, has nephrotoxic

effects, these are not identical, and the long-term contribution to CAN remains to be defined.

One way of studying the pathogenesis of CAN is to develop animal models of renal fibrosis. These have shown that fibrosis is consistently associated with upregulation of the cytokine transforming growth factor (TGF) β , a crucial regulator of extracellular matrix (ECM) turnover⁴. More detailed investigation has uncovered changes in the enzyme systems that control ECM degradation, with upregulation of the tissue inhibitors of metalloproteinases (TIMPs)⁵. These are specific inhibitors of the matrix metalloproteinases (MMPs), a group of enzymes that degrade collagen and other matrix components⁶.

Early *in vitro* work has suggested that tacrolimus, which is associated with a reduction in production of TGF- β , may be less liable to induce fibrosis than cyclosporin⁷. There is, however, little *in vivo* evidence to support this. In this experiment both cyclosporin and tacrolimus were adminis-

tered to a rodent model of renal ischaemia–reperfusion injury, which has previously been shown to be associated with upregulation of both TGF- β and TIMP-1 messenger RNA (mRNA)⁸.

Materials and methods

Experimental model

The model of renal ischaemia–reperfusion injury used in these experiments has been described previously⁸. Briefly, groups ($n=6$) of male Wistar rats (300–350 g) were anaesthetized with halothane and underwent a midline laparotomy. Both renal pedicles were exposed, allowing occlusion of the right pedicle with a vascular clamp for 45 min, together with left nephrectomy. After recovery animals were returned to their cages and followed for a period of 16 weeks.

Drug administration

Drugs were administered orally by gavage, once daily. Microemulsion cyclosporin liquid (Neoral; Novartis Pharmaceuticals, Camberley, UK) was dissolved in pure olive oil to a concentration of 5 mg/ml and administered as a daily dose of 10 mg/kg. Tacrolimus powder (Prograf; Fujisawa, London, UK) was dissolved in water to a concentration of 0.1 mg/ml and administered as a daily dose of 0.2 mg/kg. The control group of animals underwent ischaemic injury only.

Assessment of renal function and damage

Blood obtained at the time of killing was used to measure serum creatinine levels and to give an indication of renal function at 16 weeks.

Proteinuria was used as a marker of renal damage, assessed at 4-week intervals. Urinary levels of total protein (mg/l; determined by the Bradford method⁹) and creatinine ($\mu\text{mol/l}$) were measured to allow calculation of the urinary protein : creatinine ratio, which has been shown to correlate well with 24-h urinary protein concentration¹⁰.

Normal ranges for serum creatinine concentration and protein : creatinine ratio were obtained from unoperated control animals ($n=6$) that were of the same weight and housed in the same conditions.

Histological assessment

Formalin-fixed haematoxylin and eosin-stained sections of kidney were examined by a renal histopathologist and graded for tubulointerstitial fibrosis. This was done on a

blinded basis with scoring on a semiquantitative scale of 0–3, where zero was normal.

Molecular analysis

The methods used to quantify levels of mRNA expression using reverse transcriptase–polymerase chain reaction (RT-PCR) have been described previously^{11,12}. Renal cortex was isolated and homogenized, and mRNA was isolated by means of Dynabeads (Dynal, Bromborough, UK). RT-PCR was then used to amplify genes of interest, with subsequent quantification in an enzyme-linked immunosorbent assay system. Six genes were chosen for study in this experiment: TGF- β , collagen III, MMP-2, MMP-9, TIMP-1 and TIMP-2.

To allow for differences in cellularity between specimens, the housekeeping gene *GAPDH* was also amplified, and all values for gene expression were expressed as a ratio to that of *GAPDH*.

Statistical analysis

Mean values of serum creatinine concentration, urinary protein : creatinine ratio and mRNA expression were compared with Student's *t* test for independent samples.

Results

Renal function

After laparotomy all animals lost weight in the first week but this subsequently increased steadily and there were no significant differences between the groups. Serum creatinine concentration at 16 weeks was increased significantly

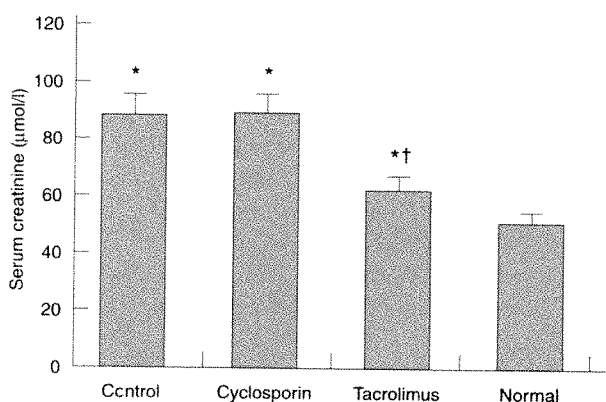


Fig. 1 Effect of drug administration on serum creatinine levels at 16 weeks. Values are mean (s.e.m.) * $P < 0.05$ versus normal; † $P < 0.05$ versus control and cyclosporin (Student's *t* test)

above baseline levels in all three groups (*Fig. 1*). However, animals in the tacrolimus-treated group had significantly lower serum creatinine levels than both untreated animals and those treated with cyclosporin. Urinary protein excretion was also increased significantly by 16 weeks in all groups (*Fig. 2*). The cyclosporin-treated group of animals was found to have markedly increased proteinuria compared with the other two groups. Although rats in the tacrolimus-treated group had less proteinuria than untreated animals, this was not statistically significant.

Histological findings

In the majority of animals tubulointerstitial fibrosis was either absent or mild (*Table 1*). None of the animals developed severe (grade 3) fibrosis.

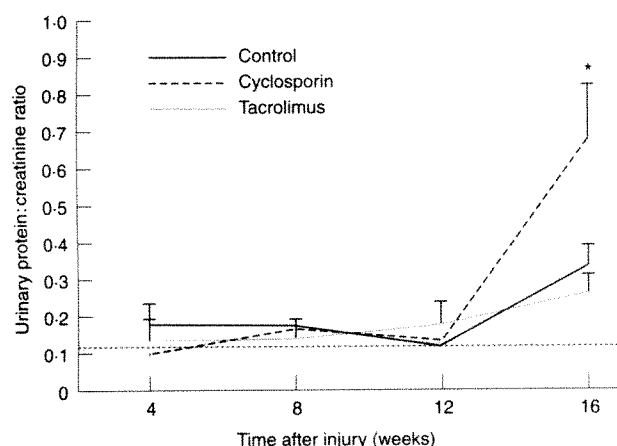


Fig. 2 Development of proteinuria. Values are mean(s.e.m.); the horizontal line shows values for the normal range. $P < 0.05$ for all three experimental groups *versus* normal range at 16 weeks; * $P < 0.05$ *versus* control and tacrolimus groups (Student's *t* test)

Table 1 Histopathological findings after renal ischaemia–reperfusion injury

	Tubulointerstitial fibrosis score			
	0	1	2	3
Control	0	4	2	0
Cyclosporin	2	2	2	0
Tacrolimus	3	2	1	0

0, Absent; 1, mild; 2, moderate; 3, severe

Gene expression

Differences in gene expression between the three groups are shown in *Fig. 3*. The most striking findings were with regard to the expression of TGF- β and TIMP-1. Administration of cyclosporin had no influence on the expression of these genes, but tacrolimus significantly reduced their expression. Cyclosporin administration did increase the expression of collagen III and reduced the expression of the matrix-degrading enzymes MMP-2 and MMP-9, but in none of these cases was the difference statistically significant. Tacrolimus did not have any effect on the expression of these genes.

Discussion

There is much interest as to whether novel immunosuppressive treatments will have any impact on CAN. While the effect of these drugs on immune damage is obviously crucial, other mechanisms are likely to be important in preventing the development of fibrosis, the characteristic feature of CAN. The model used in this experiment allows the study of how drugs influence fibrosis directly. This is in contrast to models of renal transplantation, where the immunosuppressive potency of the drug also plays a role, by influencing the effect of immune damage on the process. Hence, although this model does not reflect the clinical situation directly, it provides a method of dissecting out the mechanisms underlying the development of fibrosis.

Cyclosporin has no therapeutic effect in this model and, indeed, worsened the degree of proteinuria that developed after ischaemic injury. This is unsurprising given what is known about its direct nephrotoxic effects¹³. Tacrolimus, in contrast to cyclosporin, did not worsen the degree of proteinuria that occurred; when serum creatinine concentration at 16 weeks was compared with that in both the cyclosporin-treated and untreated groups, it was significantly reduced, suggesting that tacrolimus had a beneficial effect on renal function. There have been previous reports regarding the beneficial effects of tacrolimus in chronic renal disease^{14,15}. The effects on proteinuria and serum creatinine levels of the two drugs may well have implications for long-term dysfunction, as there is evidence that proteinuria after renal transplantation is associated with a poorer long-term prognosis¹⁶.

As well as functional variables, changes in gene expression were studied to determine whether drug treatment had any influence on the molecular mechanisms underlying fibrosis. This is likely to be of major importance as early influence on the pathways leading to fibrosis provides perhaps the best chance of retarding or preventing its development.

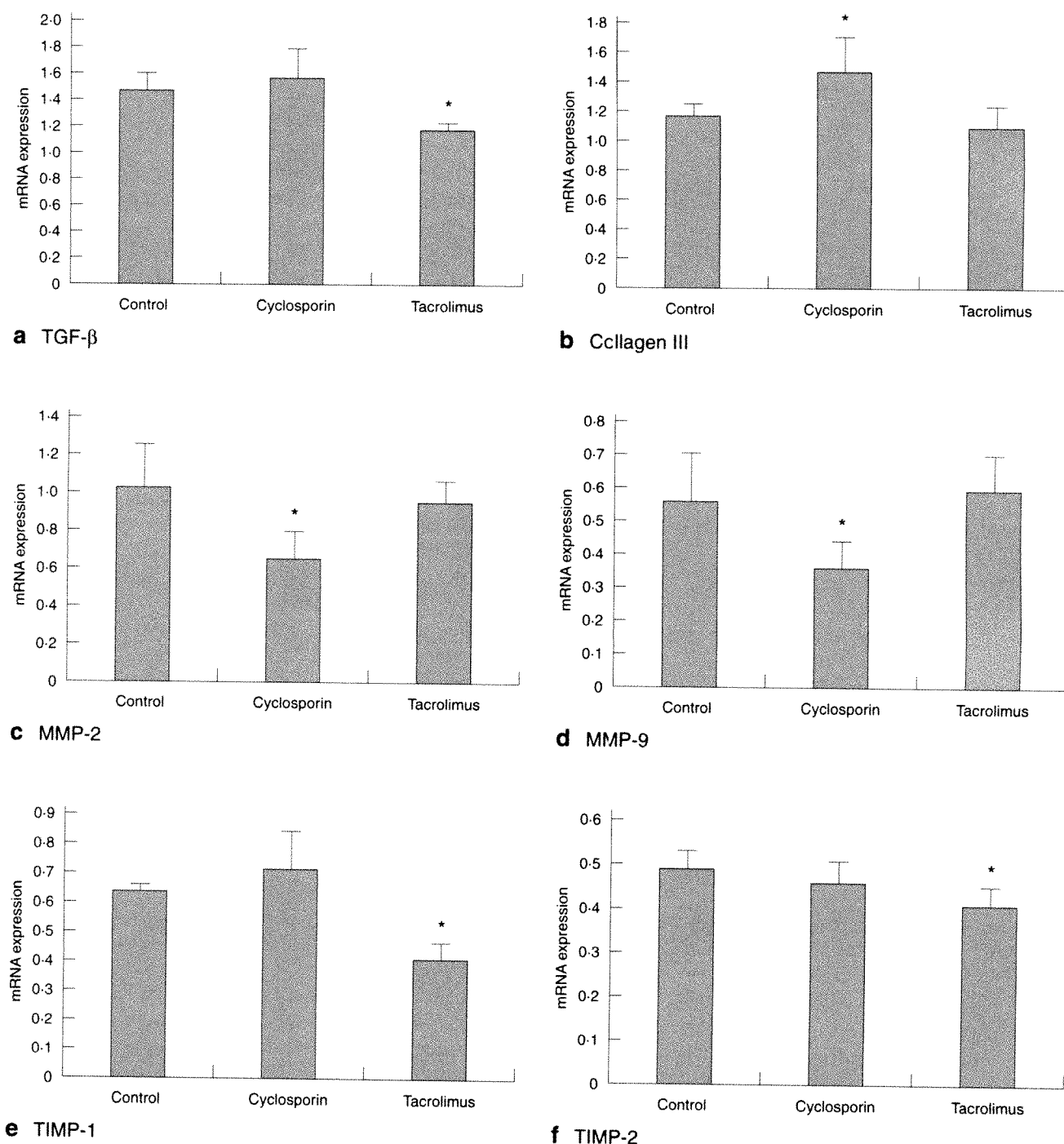


Fig. 3 Gene expression. Values are mean(s.e.m.) for messenger RNA (mRNA) expression in arbitrary units, given as a ratio to that of the housekeeping gene *GAPDH*.

a Transforming growth factor (TGF) β . * $P=0.05$ versus control; $P=0.10$ versus cyclosporin (Student's *t* test)

b Collagen III. * $P=0.25$ versus control; $P=0.18$ versus tacrolimus (Student's *t* test)

c Matrix metalloproteinase (MMP) 2. * $P=0.18$ versus control; $P=0.13$ versus tacrolimus (Student's *t* test)

d MMP-9. * $P=0.28$ versus control; $P=0.11$ versus tacrolimus (Student's *t* test)

e Tissue inhibitor of metalloproteinases (TIMP) 1. * $P=0.007$ versus control; $P=0.07$ versus cyclosporin (Student's *t* test)

f TIMP-2. * $P=0.23$ versus control; $P=0.48$ versus cyclosporin (Student's *t* test)

Tacrolimus would appear to have a beneficial effect in this regard by reducing the expression of both TGF- β and TIMP-1. Reduction of TGF- β expression is seen by many as an important future therapeutic strategy in combating fibrotic diseases. This cytokine is central to the development of renal fibrosis⁴ and has a key role in CAN¹⁷. There has been previous *in vitro* evidence that tacrolimus is less stimulatory to TGF- β than cyclosporin⁷. The *in vivo* evidence is less convincing and, indeed, Shihab *et al.*¹⁸ reported that tacrolimus increased TGF- β mRNA expression when administered to rats. The dose of tacrolimus used in this study was, however, 1 mg/kg daily, five times greater than that used in the present study, which is also that used in humans. Unfortunately as drug levels were not measured it is impossible to say whether they were in the therapeutic range. Human clinical studies measuring blood levels of TGF- β have found that tacrolimus treatment has no effect^{19,20}; as yet there are no tissue data from human studies.

TIMP-1 is an enzyme inhibitor that limits the degradation of ECM and therefore contributes to the development of fibrosis²¹. As well as being raised in this experimental model, it has been shown to be overexpressed in several other models of renal fibrosis^{22,23}. Its production is stimulated by TGF- β ²⁴ and therefore it would be expected that, like TGF- β , expression of TIMP-1 would be reduced in animals treated with tacrolimus. A change in the expression of TIMP-1 cannot be viewed in isolation, as the breakdown of ECM will be based on its relative abundance compared with that of the MMPs. The expression of MMP-2 and MMP-9 was not raised by tacrolimus therapy, suggesting there is a genuine shift in the balance of ECM turnover. Interestingly, cyclosporin therapy reduced expression of both MMPs, although this was not statistically significant.

None of the animals in this experiment developed severe fibrosis, suggesting that changes in gene expression had not yet translated into significant increased ECM deposition. The tacrolimus-treated group included more animals in which fibrosis was absent, although the significance of this is uncertain as grading was semiquantitative. Current studies are looking at ways to quantify levels of ECM accurately in an effort to see whether there are any subtle changes that can be detected at this early stage.

One possible reason for the differences between the groups may relate to the degree of proteinuria. It has been documented in several models that prolonged proteinuria leads to the development of interstitial fibrosis, and studies of the molecular biology have revealed upregulation of both TGF- β and TIMP-1²⁵. In this experiment tacrolimus certainly led to a reduced amount of proteinuria, but it is obviously impossible to prove causality from the available data.

These animals did not develop severe histological changes of renal fibrosis, and ultimately differences in the degree of fibrosis will be used to judge the benefits of any new drugs. Changes in gene expression may be a surrogate early marker of gross histological fibrosis, but confirmation will require longer follow-up.

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Differential effects of cyclosporin and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants

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Background: Chronic allograft nephropathy is characterized by an excessive accumulation of extracellular matrix proteins leading to glomerular and interstitial fibrosis. The aim of this study was to determine the effects of two different immunosuppressive agents (cyclosporin and tacrolimus) on the expression of the genes controlling extracellular matrix deposition in renal transplant glomeruli.

Methods: Fifty-one renal transplant recipients were randomized to receive immunosuppression with either microemulsion cyclosporin or tacrolimus. Isolated glomeruli were plucked from protocol transplant biopsies performed 1 week, 3 months and 6 months after transplantation. Expression of the genes for collagen IV α 2, collagen III, matrix metalloproteinase 2, tissue inhibitor of metalloproteinases (TIMP) 1 and TIMP-2, tenascin and transforming growth factor (TGF) β 1 was studied by quantitative reverse transcriptase-polymerase chain reaction.

Results: The expression of messenger RNA (mRNA) for collagen III and TIMP-1 was significantly higher in patients receiving cyclosporin therapy than in those having tacrolimus ($P < 0.01$); this finding was accounted for by differences in the biopsy material at 1 week. A significant difference in collagen III, TIMP-1 and TIMP-2 mRNA expression was also detected between patients depending on the source of renal donor (cadaveric or living). There were no significant differences in the level of glomerular TGF- β 1.

Conclusion: The data provide new *in vivo* evidence that tacrolimus may exert a less fibrogenic influence on transplant glomeruli than cyclosporin.

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Introduction

Chronic allograft nephropathy (CAN) continues to be one of the commonest causes of late kidney transplant failure^{1–3}. Although the pathophysiology of this process is complex, it is clear that CAN results from the kidney's stereotyped fibrotic response to a variety of early ischaemic, immunological and toxic insults⁴. The nephrotoxic properties of the various immunosuppressive drugs are also likely to be an important influence, but the differential effects of the calcineurin inhibitors cyclosporin and tacrolimus remain unclear. Tacrolimus has been shown to be a successful rescue therapy in some failing allografts⁵ and a number of studies have demonstrated that its use is associated with lower acute rejection than is found with cyclosporin^{6,7}. Given that acute rejection is an important predictor of the

subsequent development of CAN^{8,9}, it has been suggested that tacrolimus may have beneficial effects on long-term renal allograft half-life¹⁰.

The histopathology of chronically failing renal transplants is dominated by glomerulosclerosis and interstitial fibrosis. Glomerulosclerosis results from the deposition of abnormal amounts of extracellular matrix within the glomeruli, eventually leading to their complete obliteration. This is one of the primary causes of the progressive and irreversible reduction of renal function that characterizes CAN. The accumulation of extracellular matrix proteins is of considerable complexity, determined not only by the rate of synthesis of the collagens and glycoproteins, but also by the rate of their degradation¹¹. The degradative side of the balance is under the control of the proteolytic matrix metalloproteinases (MMPs), which in turn are regulated by

Table 1 Primer and probe sequences

	5' (Forward) primer		3' (Reverse) primer		ELISA probe	
GAPDH	AGAACATCAT	CCCTGCCTC	GCCAAATTCG	TTGTCATACC	GTTGAAGTCA	GAGGAGACC
Collagen IV α 2	CATGAAAGGT	CTCTCTGGTG	GTATTCGGAA	AAATCCAGC	CTTTGCTCCC	TGGAAACCCG
Collagen III	CCTGGTACAT	CTGGTCATCC	CCATTTCAC	CCTTTAATCC	ACCAGATGGA	CCTATAGCAC
MMP-2	ATTGATGCGG	TATACGAGGC	GGCACCCCTTG	AAGAAGTAGC	CTCCAGAATT	TGTCTCCAGC
TIMP-1	TGGGGACACC	AGAAGTCAAC	CAGGGGATGG	ATAAACAGGG	GTAGTGATGT	GCAAGAGTCC
TIMP-2	AACGACATTT	ATGGCAACCC	ACCTGTGGTT	CAGGCTCTTC	TCTATATCCT	TCTCAGGCC
Tenascin	TGAACAAAAT	CACAGCCAG	CAGTGAACC	AGTTAACGCC	TGATGGCTGA	ATCTGTGTCC
TGF- β 1	AAGTTAAAAG	TGGAGCAGC	CACCTGCAGT	GTGTTATCC	CGGTGACATC	AAAAGATAAC

ELISA, enzyme-linked immunosorbent assay; GAPDH, glyceraldehyde phosphate dehydrogenase; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; TGF, transforming growth factor

Table 2 Clinical characteristics of patients in the cyclosporin versus tacrolimus trial

	Cyclosporin	Tacrolimus	P
Mean age of recipient (years)	45	43	0.28‡
Sex ratio (M:F)	15:7	18:11	0.44§
Mean age of donor (years)	43	43	0.50‡
Donor source			
Living	4	5	0.61§
Cadaveric	9	13	0.50§
Non-heart-beating	9	11	0.53§
HLA-DR mismatch			
0 versus 1 or 2	9:13	13:16	0.53§
Mean cold ischaemia time (h)	13.7	12.6	0.34‡
Acute rejection*	6 of 22	7 of 29	0.53§
Delayed graft function†	9 (3)	9	0.33§

HLA, human leucocyte antigen. *Rejection occurring in the first 3 months after transplantation. †Value in parentheses indicates additional primary non-functioning transplants. ‡Mann-Whitney *U* test. §Fisher's exact test; with donor source, each source was tested, in turn, against the other two combined

their own tissue inhibitors (TIMPs). A number of cytokines and growth factors are involved, of which transforming growth factor (TGF) β is thought to be especially important^{12,13}.

The aim of this study was to determine the effects of cyclosporin and tacrolimus on the expression of genes controlling extracellular matrix deposition in isolated glomeruli from renal transplants.

Patients and methods

Therapeutic protocol

A consecutive series of renal transplant recipients were randomly allocated to receive an immunosuppressive regimen based on either microemulsion cyclosporin or

tacrolimus. Randomization was performed in a 1:1 ratio using a system of codes, generated from a table of random numbers, and sealed envelopes. The detailed immunosuppressive protocol was varied according to the source of the donor kidney. Recipients of transplants from heart-beating cadaveric and living donors received either microemulsion cyclosporin (Neoral; Novartis, Camberley, UK) at a starting dose of 15 mg/kg daily or tacrolimus (Prograf; Fugisawa, London, UK) at a starting dose of 0.2 mg/kg daily. The cyclosporin dose was reduced by 2 mg/kg per week to a baseline level of 5 mg/kg daily by week 6 after transplantation, but this protocol was also adjusted carefully to maintain trough whole-blood cyclosporin levels between 200 and 300 ng/ml in the first 3 months and 150–250 ng/ml thereafter. Tacrolimus dosage was also adjusted to maintain whole-blood trough levels of 8–15 ng/ml. The recipients of transplants from a non-heart-beating donor (NHBD) received either cyclosporin 7 mg/kg daily, reduced to 5 mg/kg daily after 1 week, or tacrolimus 0.1 mg/kg daily. All patients received prednisolone at a daily dose of 20 mg for the first 3 months, with a gradual reduction to 10 mg on alternate days by 6 months. Recipients of NHBD transplants also received azathioprine 1 mg/kg daily. All patients entering the trial had protocol renal transplant biopsies performed under real-time ultrasonographic control at 1 week, 3 months and 6 months post-transplant.

Isolation of glomeruli and extraction of messenger RNA

Two individual glomeruli were plucked from fresh renal biopsies and the messenger RNA (mRNA) from each was extracted and processed separately with oligo-deoxythymidine (dT)-linked Dynabeads (Dynal, Bromborough, UK), as described previously¹⁴.

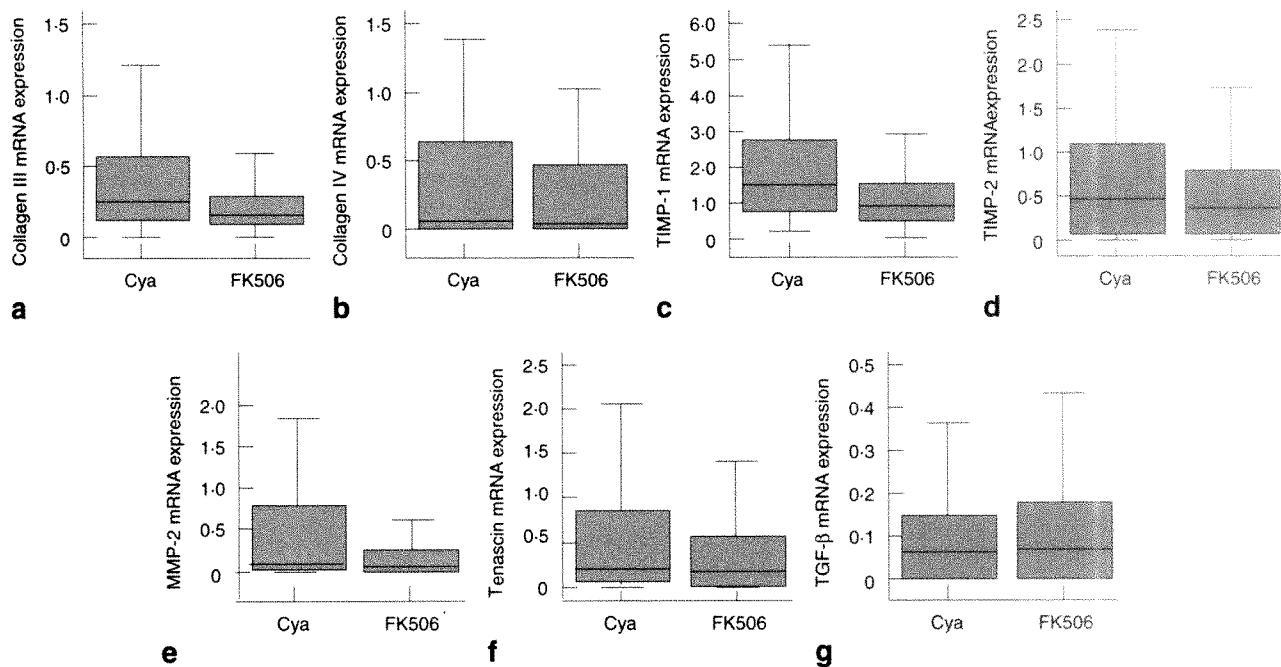


Fig. 1 Expression of messenger RNA (mRNA) in patients immunosuppressed by cyclosporin (CyA) or tacrolimus (FK506). mRNA expression is represented by arbitrary units of absorbance at 405 nm, as defined in Patients and methods.

- a** Collagen III ($P=0.004$, Mann–Whitney U test)
b Collagen IV ($P=0.49$, Mann–Whitney U test)
c Tissue inhibitor of metalloproteinases (TIMP) 1 ($P=0.001$, Mann–Whitney U test)
d TIMP-2 ($P=0.20$, Mann–Whitney U test)
e Matrix metalloproteinase (MMP) 2 ($P=0.16$, Mann–Whitney U test)
f Tenascin ($P=0.23$, Mann–Whitney U test)
g Transforming growth factor (TGF) β ($P=0.59$, Mann–Whitney U test)

Reverse transcriptase–competitive polymerase chain reaction

This was performed essentially as published^{14,15}. In competitive polymerase chain reaction (PCR) experiments, 18 fg of competitor DNA was added to the reaction mixture. The competitor DNA was constructed as detailed¹⁵. All PCR products were screened by agarose gel electrophoresis to confirm that the efficiency of each reaction had not been compromised by contamination of reagents (including contamination of mRNA by pseudogenes and other genomic DNA). All primers and probes were designed in-house as already described, but for convenience they are listed in Table 1. Where possible, primers were designed to span introns. Primers and probes were synthesized by Life Technologies (Paisley, UK) or GenoSys Biotechnologies Europe (Pampisford, UK). Forward primers were synthesized 5'-biotinylated to enable capture of forward strand complementary DNA (cDNA) during enzyme-linked immunosorbent assay (ELISA).

Measurement of polymerase chain reaction products

A digoxigenin–alkaline phosphatase ELISA system was employed to detect and quantify the reverse transcriptase (RT)–PCR reaction products^{14,15}, but it was modified to use 1 per cent bovine serum albumin in phosphate-buffered saline as a blocking agent. ELISA measurements were performed in duplicate with controls for non-specific probe binding, probe efficiency and plate quality. Mean results were corrected for glomerular cellularity using the observed ratio of glyceraldehyde phosphate dehydrogenase cDNA (a constitutively expressed gene) to competitor DNA¹⁵.

Statistical analysis

Two-tailed non-parametric analysis of variance (Mann–Whitney U test or Kruskal–Wallis H test) was performed by the SPSS program (SPSS, Chicago, Illinois, USA) using ELISA results normalized for ELISA probe variation and glomerular cellularity.

Table 3 Quantification of messenger RNA levels by enzyme-linked immunosorbent assay

	Cyclosporin*	Tacrolimus*	P†
Collagen IVα2			
1 week	0.160	0.297	0.731
3 months	0.082	0.073	0.899
6 months	0.005	0.000	0.233
Collagen III			
1 week	0.294	0.156	<0.001
3 months	0.187	0.161	0.452
6 months	0.249	0.175	0.733
MMP-2			
1 week	0.190	0.218	0.440
3 months	0.119	0.021	0.282
6 months	0.039	0.023	0.645
TIMP-1			
1 week	1.755	0.781	≤ 0.001
3 months	1.192	0.930	0.122
6 months	1.108	0.885	0.426
TIMP-2			
1 week	0.481	0.518	0.518
3 months	0.480	0.254	0.095
6 months	0.297	0.270	0.805
Tenascin			
1 week	0.590	0.509	0.408
3 months	0.147	0.113	0.901
6 months	0.075	0.035	0.373
TGF-β1			
1 week	0.086	0.092	0.341
3 months	0.058	0.104	0.689
6 months	0.026	0.009	0.322

*Values are median. MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; TGF, transforming growth factor.

†Mann-Whitney *U* test

Results

The clinical characteristics of the 51 patients studied are shown in Table 2. Twenty-two patients received cyclosporin based immunosuppression and 29 received tacrolimus. The two groups were well matched for recipient age, sex ratio, donor age, donor source, human leucocyte antigen (HLA)-DR mismatch and cold ischaemia time.

The level of mRNA expression for collagen III and TIMP-1 was significantly higher in cyclosporin- than in tacrolimus-treated patients ($P < 0.01$) (Fig. 1). There were no significant differences in the levels of mRNA expression for collagen IV α 2, MMP-2, TIMP-2, tenascin and TGF- β 1. Analysis over time showed that the differences in collagen III and TIMP-1 mRNA expression were attributable to the results at 1 week post-transplant ($P \leq 0.001$) (Table 3). There were no significant differences in mRNA expression 3 and 6 months after transplantation. The authors have reported previously that the use of NHBKD kidneys may affect TIMP-1 expression¹⁶. In the present

study, donor type was found to influence the expression of mRNA for collagen III, TIMP-1 and TIMP-2 (Fig. 2). Subgroup analysis demonstrated that kidney transplants from living donors treated with cyclosporin had an increased expression of collagen III mRNA ($P = 0.02$) (Fig. 3), and transplants from cadaveric donors (heart-beating and NHB) treated with tacrolimus had a decreased expression of TIMP-1 mRNA ($P = 0.05$) (Fig. 3). Living donor transplants exhibited lower TIMP-2 mRNA expression than heart-beating donor or NHBKD transplants (Fig. 2), primarily due to the effects of cyclosporin (Fig. 3). Additionally, living and NHB donor transplants immunosuppressed with tacrolimus showed decreased collagen IV α 2 mRNA expression compared with their heart-beating cadaveric counterparts ($P = 0.02$).

Discussion

This study is the first to demonstrate different patterns of glomerular gene expression in renal transplant recipients immunosuppressed with either cyclosporin or tacrolimus. The findings suggest that microemulsion cyclosporin may exert a more fibrogenic influence on glomeruli than tacrolimus. Donor source also appeared to have an influence on the expression of some of the genes under study, but only small numbers of living donor transplants were included. Although it cannot be stated that individually isolated glomeruli were normal (isolation precluded use in histological examination), patients' clinical characteristics were unlikely to introduce bias into the degree of any sclerosis, as characteristics of patients in the two drug groups were not significantly different.

The genes of interest were chosen to try to represent the balance of forces in the fibrotic process. Extracellular matrix is constantly remodelled and a steady state exists only if the synthesis of the collagens is balanced by expression of their appropriate MMPs. Upregulation of the mRNA for TIMPs is a profibrotic influence as these molecules inhibit the enzymes responsible for degrading excess collagen and may even induce effects more commonly associated with growth factors^{17,18}. An increase in expression of TIMPs can therefore lead to increased collagen deposition in the matrix.

TIMP-1 primarily inhibits MMP-9, whereas TIMP-2 primarily inhibits MMP-2; there is, however, a degree of overlap in these actions^{16,19,20}. Both metalloproteinases are classed as type IV collagenases, although MMP-2 degrades a broader range of other collagens, including type III. Because collagen IV α 2 is relatively specific to the glomerular basement membrane, the concomitant increase in TIMP-1, TIMP-2 and collagen III mRNA

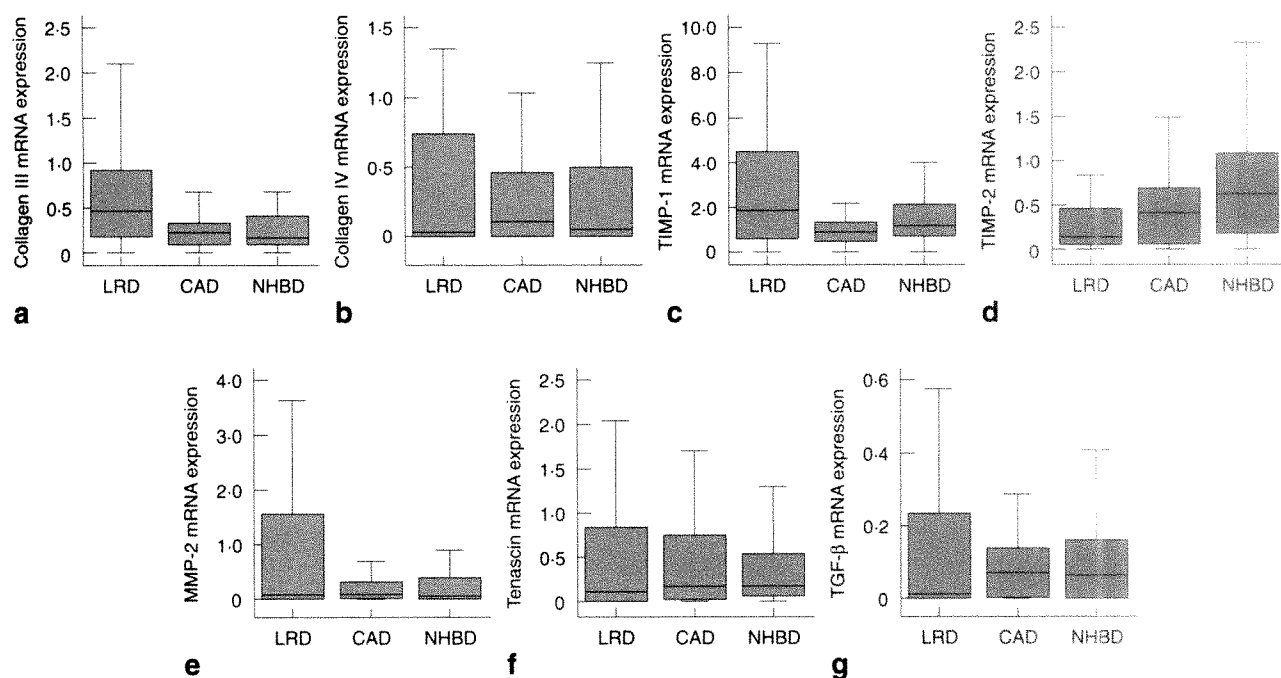


Fig. 2 Expression of messenger RNA (mRNA) in patients receiving a transplant from a living renal donor (LRD), a heart-beating cadaver (CAD) and a non-heart-beating donor (NHBD), pooled from all time points. mRNA expression is represented by arbitrary units of absorbance at 405 nm, as defined in Patients and methods.

a Collagen III ($P = 0.012$, Kruskal–Wallis H test)

b Collagen IV ($P = 0.73$, Kruskal–Wallis H test)

c Tissue inhibitor of metalloproteinases (TIMP) 1 ($P = 0.019$, Kruskal–Wallis H test)

d TIMP-2 ($P = 0.007$, Kruskal–Wallis H test)

e Matrix metalloproteinase (MMP) 2 ($P = 0.51$, Kruskal–Wallis H test)

f Tenascin ($P = 0.74$, Kruskal–Wallis H test)

g Transforming growth factor (TGF) β ($P = 0.92$, Kruskal–Wallis H test)

expression would effectively represent a triple insult for the matrix, with net deposition subsequently occurring of both collagen III and collagen IV α 2, despite any potential increase in MMP-2 expression.

The role of MMP-9 was not fully investigated in this study but, given the significant expression of TIMP-1 and its induction only in glomerular disease²¹, future work will need to address this omission. Further candidates for study would also be MMP-3 and MMP-1, which act on procollagen and mature collagen III respectively²², and collagen IV α 5²³.

An advantage of the techniques described here is that they use bead-linked cDNA libraries to obtain the data on mRNA expression. This ensures that further investigations can be made at any time without the need to start a new trial. Preliminary results have shown that cyclosporin-treated patients do not exhibit significantly different levels of MMP-9 or inducible nitric oxide synthase mRNA (unpublished observations).

TGF- β acts in a variety of ways that can be expected to lead to increased deposition of extracellular matrix, and previous studies have demonstrated a correlation between the expression of TGF- β mRNA and interstitial fibrosis^{11,12,24}. Although TGF- β 1 expression was demonstrated in glomeruli at all three of the time points studied, the levels diminished with time and there were no significant differences between the two drug groups or between the different donor groups. Cyclosporin has been shown to upregulate TGF- β production at both the mRNA and protein levels²⁵ but there is some evidence that tacrolimus does not produce the same effect²⁶.

The present observations regarding TGF- β expression relate only to the glomeruli and are not necessarily inconsistent with findings in previous studies. This is especially so as most of the early intragraft TGF- β is likely to come from circulating platelets and macrophages that infiltrate the interstitium. Perhaps most importantly in the context of this study, tacrolimus competes with the TGF- β 1

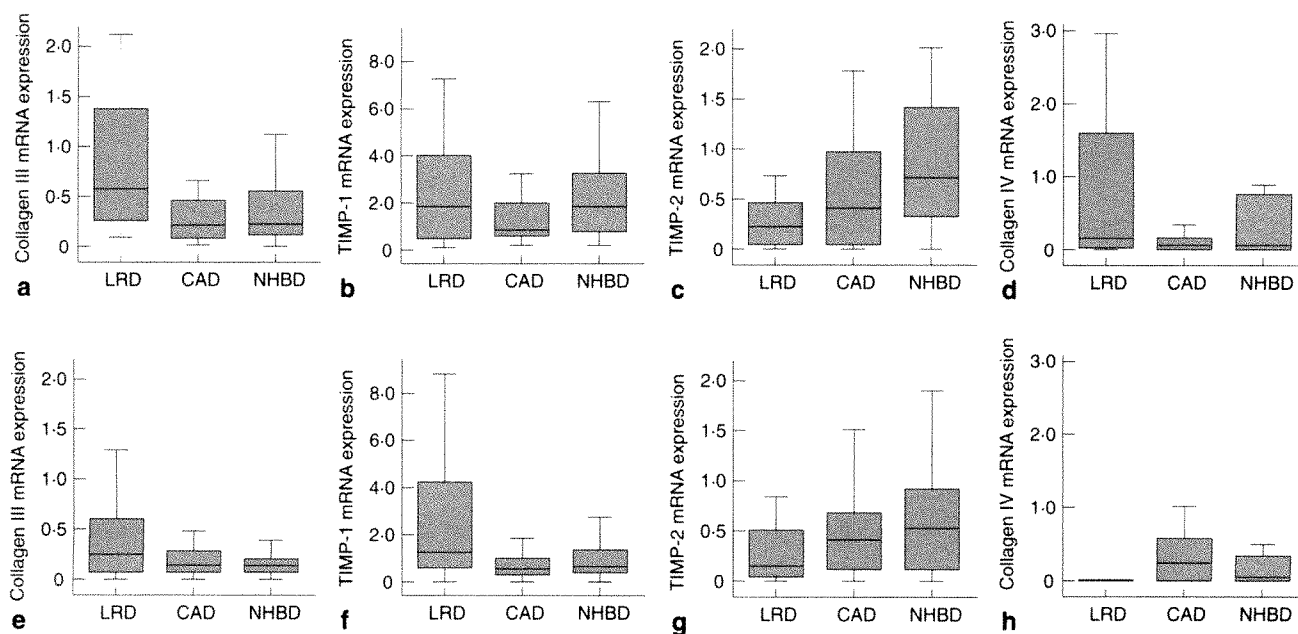


Fig. 3 Expression of messenger RNA (mRNA) in patients receiving a transplant from a living renal donor (LRD), a heart-beating cadaver (CAD) and a non-heart-beating donor (NHBD), immunosuppressed by **a–d** cyclosporin or **e–h** tacrolimus, pooled from all time points. mRNA expression is represented by arbitrary units of absorbance at 405 nm, as defined in Patients and methods.

a Collagen III. $P = 0.021$ (Kruskal–Wallis H test); $P = 0.006$ (LRD versus CAD and NHBD, Mann–Whitney U test)

b Tissue inhibitor of metalloproteinases (TIMP) 1. $P = 0.17$ (Kruskal–Wallis H test)

c TIMP-2. $P = 0.021$ (Kruskal–Wallis H test); $P = 0.046$ (LRD versus CAD and NHBD, Mann–Whitney U test)

d Collagen IV. $P = 0.29$ (Kruskal–Wallis H test)

e Collagen III. $P = 0.39$ (Kruskal–Wallis H test)

f TIMP-1. $P = 0.052$ (Kruskal–Wallis H test); $P = 0.33$ (CAD and NHBD versus LRD, Mann–Whitney U test)

g TIMP-2. $P = 0.22$ (Kruskal–Wallis H test)

h Collagen IV. $P = 0.028$ (Kruskal–Wallis H test); $P = 0.017$ (LRD and NHBD versus CAD, Mann–Whitney U test)

receptor for binding to FKBP-12, making TGF- β in the graft potentially less effective²⁷. It may be that, without this advantage, the levels of collagen III and TIMP-1 mRNA would be as high in tacrolimus-treated patients as they were in their cyclosporin-treated counterparts.

It should be stressed that an increase in mRNA expression does not *per se* demonstrate increased deposition of matrix, since there are many steps between the synthesis of mRNA and the final expression of (active) protein. Although other laboratories have demonstrated an association between the mRNA expression of TIMPs and the degree of glomerulosclerosis²⁸, no attempt was made to quantify this in the present study as the protocol biopsies were taken at relatively early time points after transplantation when excessive extracellular matrix deposition would not be expected to have occurred.

Confirmation that cyclosporin and tacrolimus exert a different degree of fibrogenicity in renal transplant

glomeruli will need the long-term follow-up of large numbers of patients. Notwithstanding this, studies are in progress to address collagen III deposition in biopsies taken at 6 months²⁹, with a view to correlating the results both with this study and with the final graft survival times. In the interim, the estimation of mRNA expression has certain advantages over the determination of protein content, including better quantification of the rate of synthesis and a vastly reduced requirement for starting material. The ability to detect changes in gene expression long before their effects become apparent histologically might provide invaluable surrogate markers for the development of CAN.

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Jejunal interposition to prevent postgastrectomy syndromes

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Background: Postgastrectomy syndromes include reflux gastritis and oesophagitis, dumping syndrome, intractable diarrhoea and afferent loop syndrome. To prevent such syndromes, since January 1994 jejunal interposition has been used following distal gastrectomy. The aim of this study was to evaluate the benefit of this procedure.

Methods: A consecutive series of 42 patients who underwent distal gastrectomy for gastric cancer was studied. Twenty-two patients had a Billroth I procedure before January 1994, and 20 patients had isoperistaltic jejunal interposition using a 10–12-cm segment after January 1994.

Results: The mean operating time was 260 min for Billroth I and 352 min for jejunal interposition. No serious postoperative complications arose. Reflux gastritis occurred in 19 patients after Billroth I but in none after jejunal interposition. Five patients in the Billroth I group had complaints consistent with dumping syndrome, compared with none after jejunal interposition. The barium gastric emptying time was significantly shorter after Billroth I (mean(s.d.) 269(225) s) than after jejunal interposition (736(479) s) ($P < 0.01$).

Conclusion: Jejunal interposition prevented reflux gastritis and inhibited rapid gastric emptying. Postgastrectomy syndromes were effectively prevented by this reconstruction procedure.

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Introduction

Recent progress in the diagnosis and surgical treatment of early gastric cancer has markedly reduced the mortality rate. In Japan, 5-year survival rates in patients receiving curative resection for early gastric cancer exceed 90 per cent^{1,2}. More attention should be focused on symptom relief to improve the quality of life for long-term survivors. Postoperative clinical issues include alkaline reflux gastritis, early and late dumping syndrome, intractable diarrhoea and afferent loop syndrome following gastrectomy: the postgastrectomy syndromes. Bile reflux gastritis is found endoscopically in almost all patients who undergo Billroth I and II procedures. Reflux of bile acids into the gastric remnant is associated with a risk of carcinoma³. Experimental studies have demonstrated that primary duodenogastric reflux can induce gastric carcinogenesis⁴.

The dumping syndrome occurs in 13–58 per cent of patients following gastrectomy^{5,6}. The vasomotor symptoms of dumping syndrome are presumably caused by rapid gastric emptying and small intestinal transit. Although the symptoms often improve with time, medical management

or dietary manipulation, remedial surgery is occasionally required.

The authors often encountered patients treated by Billroth I repair in whom daily life was disturbed by postgastrectomy syndromes. Therefore, since January 1994, isoperistaltic jejunal interposition has been used following distal gastrectomy. This study was a retrospective evaluation of the benefits of this procedure.

Patients and methods

This study included 42 patients who underwent distal gastrectomy with lymph node dissection for gastric cancer at the Arita Gastrointestinal Hospital between January 1992 and June 1998. Twenty-two patients treated before January 1994 had a Billroth I repair and 20 patients treated after January 1994 underwent jejunal interposition. The postoperative results were compared between the two groups.

Jejunal interposition was performed as follows: a 10–12-cm section of jejunum, which was prepared at a point 20 cm distal from the ligament of Treitz, was brought through the

transverse mesocolon and anastomosed in an isoperistaltic orientation to the greater curvature of the stomach and duodenum with a single layer of interrupted silk sutures. Both gastrojejunal and jejunoduodenal anastomoses were performed end to end (Fig. 1).

Information on each patient's age, sex and operative complications was obtained retrospectively from the medical chart. Operation records provided data on operating time and blood loss. Assessment of postoperative function after 1 year included an evaluation of body-weight change, and measurement of haemoglobin, total protein and total cholesterol concentrations. Barium was used to calculate gastric remnant emptying time by radiographic observation. The presence of dumping syndrome was assessed via self-reporting. Reflux gastritis and oesophagitis were assessed endoscopically according to the degree of epithelial redness and erosion.

Results were expressed as mean(s.d.) and the statistical significance of differences between the two groups was determined by Mann-Whitney *U* test and Fisher's exact test. $P < 0.05$ was considered significant.

Results

The clinical details in the two groups were similar (Table 1), as was the mean tumour diameter. The mean duration of

operation was significantly shorter ($P < 0.01$) and the blood loss significantly less ($P < 0.05$) after Billroth I than after jejunal interposition. No serious postoperative complications occurred. Two patients in the Billroth I group had a minor complication; one had minor anastomotic leakage that was cured by conservative therapy within 1 week and the other had a wound infection. Five patients in the jejunal interposition group had a minor complication: gastric phytobezoar was observed in three at endoscopy, wound infection in one and cholecystitis in one patient. There was no anastomotic leakage after jejunal interposition.

The mean body-weight ratio 1 year after operation compared with preoperative body-weight was 89 per cent after Billroth I and 92 per cent after jejunal interposition (P not significant; Table 2). Bile reflux gastritis was found by endoscopy in 19 patients after Billroth I but in none after jejunal interposition. Severe reflux oesophagitis (more than grade C according to the Los Angeles Classification⁷) was identified in two patients after Billroth I. Five patients reported symptoms consistent with the dumping syndrome after Billroth I; three reported sweating and tachycardia 30 min after meals and two reported sweating and fatigue approximately 2 h after meals. No patient reported symp-

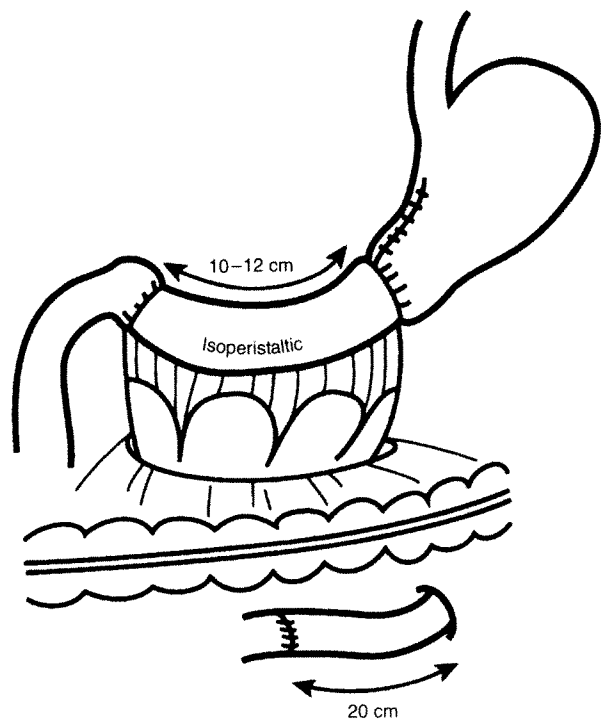


Fig. 1 Jejunal segment interposed isoperistaltically between the greater curvature of the stomach and duodenum. The jejunal segment is 10–12 cm in length

Table 1 Clinical details

	Billroth I (n=22)	Jejunal interposition (n=20)	P
Age (years)	56 (37–71)	57 (42–74)	n.s.†
Sex ratio (M:F)	13:9	14:6	n.s.*
Tumour diameter (mm)	33(20) (4–90)	38(20) (7–78)	n.s.†
Duration of operation (min)	260(40) (195–320)	352(109) (168–555)	<0.01†
Blood loss (ml)	296(152) (88–695)	417(188) (134–789)	<0.05†

Values are mean(s.d.) (range). n.s., Not significant. *Fisher's exact test; †Mann-Whitney *U* test

Table 2 Postoperative evaluation

	Billroth I (n=22)	Jejunal interposition (n=20)	P
Ratio of body-weight change (%)*	89(8)	92(7)	n.s.†
Reflux gastritis (endoscopy)	19	0	<0.01*
Reflux oesophagitis (endoscopy)	2	0	n.s.*
Dumping syndrome	5	0	<0.05*
1-year results			
Haemoglobin (g/dl)*	13.2(1.4)	13.8(1.1)	n.s.†
Total protein (g/dl)*	7.0(0.6)	7.2(0.5)	n.s.†
Total cholesterol (mg/dl)*	195(32)	192(47)	n.s.†

*Values are mean (s.d.). n.s., Not significant. *Fisher's exact test; †Mann-Whitney *U* test

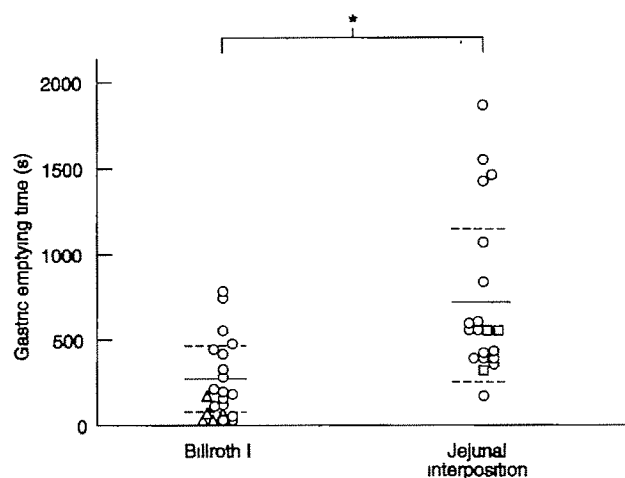


Fig. 2 Barium gastric emptying time after Billroth I repair (mean(s.d.) 269(225) s) and isoperistaltic jejunal interposition (736(479) s). Solid lines represent the mean and broken lines the standard deviation. Δ , Patients with dumping; $\square$, patients with bezoars; $\circ$, remaining patients. * $P < 0.01$, Mann-Whitney *U* test

toms after meals following jejunal interposition. Serum haemoglobin, total protein and total cholesterol levels 1 year after operation were similar between the groups (Table 2). The mean gastric emptying time was significantly shorter after Billroth I than after jejunal interposition ($P < 0.01$), especially in the five patients who reported symptoms consistent with the dumping syndrome (Fig. 2).

Discussion

Curative surgery for patients with early gastric cancer results in a favourable prognosis for long-term survival. More attention could focus on symptom relief to improve the quality of life in survivors. The Roux-en-Y gastro-jejunosomy is one method for preventing alkaline reflux gastritis, but is associated with a high incidence of the 'Roux-en-Y stasis syndrome', which consists of abdominal pain and distension, epigastric fullness, nausea and vomiting⁸. This procedure also has the disadvantage of nutrient malabsorption, such as deficiency of iron, vitamin B₁₂ and folate, caused by the lack of mixing of chyme and pancreaticobiliary secretions⁹.

Jejunal interposition between the gastric remnant and the duodenum (gastrojejunoduodenostomy) was first described by Henley¹⁰. Several other authors^{11–13} have reported the use of jejunal interposition for prevention of reflux gastritis and oesophagitis. The optimal length of the interposed segment continues to be controversial. Henley's original article described a short jejunal segment (11–13 cm); some researchers report abolition of reflux gastritis using longer

segments (greater than 20 cm). In the present study, using a short segment, endoscopic examination found no reflux gastritis, but gastric phytobezoar was observed in three patients in the early postoperative period. This was treated successfully with cisapride. Gastric stasis may be greater using a long jejunal segment.

The dumping syndrome occurs in 13–58 per cent of patients after gastrectomy^{5,6}, but can be relieved by jejunal interposition^{11,12,14,15}. In this study, the gastric emptying time using barium was significantly slower after jejunal interposition than Billroth I repair. When antiperistaltic jejunal interposition was used to delay gastric emptying the use of a 10-cm segment produced unsatisfactory results¹⁵. Since there is only a minor difference between the inhibition of rapid gastric emptying and gastric stasis, the length of interposed segment and the choice of isoperistaltic or antiperistaltic interposition may be crucial.

Reconstruction with jejunal interposition needs three anastomoses compared with one in a Billroth I procedure. This resulted in operation times and intraoperative blood loss that were greater after jejunal interposition, but without serious postoperative complications including anastomotic leakage. Gastric phytobezoar was observed in three patients during the early postoperative stage, but was not seen at 1-year follow-up. The gastric emptying time in these three patients was not delayed compared with that in the other patients after jejunal interposition.

It is possible that jejunal interposition should be the standard reconstruction following distal gastrectomy. Since 1 year is a short interval, it is intended to reinvestigate after 3 years of follow-up. Furthermore, to prove the value of jejunal interposition, it will be necessary to compare it not only with Billroth I repair but also with Roux-en-Y reconstruction, in a prospective controlled trial.

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Role of resection and primary anastomosis of the left colon in the presence of peritonitis

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Background Classically a primary colonic anastomosis is not performed in the presence of left colonic peritonitis. Recently there has been a trend towards resection and anastomosis in selected patients, but no prospective study concerning the safety of this approach has been published. The objective of this study was to define the role of intraoperative colonic lavage with resection and primary anastomosis (RPA) in left colonic peritonitis, and to evaluate the differences in outcome in patients with diffuse or localized peritonitis.

Methods: Between January 1994 and December 1998, 127 patients underwent emergency operation for a distal large bowel perforation. RPA was the operation of choice and was performed in 61 patients, 38 with localized and 23 with diffuse peritonitis. Septic shock, faecal peritonitis, immunocompromised status and American society of Anesthesiologists grade IV were contraindications to the one-stage procedure. Alternative operations used in high-risk patients were Hartmann's procedure in 55 patients, subtotal colectomy in eight and colostomy in three.

Results: There were two deaths (3 per cent) among 61 patients treated by RPA and one (2 per cent) case of clinical anastomotic dehiscence. Overall morbidity was 39 per cent and the overall mean(s.d.) hospital stay was 18(15) days. No statistical differences were observed between patients with localized and diffuse peritonitis treated by RPA.

Conclusion: RPA may be the operation of choice in selected patients with left colonic diffuse peritonitis.

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Introduction

Large bowel perforation is an abdominal emergency associated with high morbidity and mortality rates^{1,2}. Age, American Society of Anesthesiologists (ASA) grade, the presence of septic shock or concurrent major medical disease on admission have been shown to predict post-operative mortality risk^{3–5}. Peritoneal contamination by bacteria may lead to septic shock⁶, and surgical intervention must aim to prevent or treat this by removal of the septic focus. The optimal surgical approach to complicated left colonic disease remains controversial. Hartmann's procedure has gained in popularity as an alternative to the classical three-stage procedure^{7,8} and, currently, it is most commonly used for managing patients who require

emergency surgery. This staged operation has disadvantages for the patient. A second hospital admission and operation are required to re-establish intestinal continuity. Furthermore, a large proportion of patients may never proceed to reversal of Hartmann's procedure⁹. A single-stage operation that provides definitive treatment for left colonic perforation and thus avoids the disadvantages of Hartmann's operation would be the ideal therapeutic option.

Intraoperative colonic lavage with resection and primary anastomosis (RPA) has been proposed as a safe and expedient method for single-stage resection and anastomosis. It is widely accepted as a safe procedure for treatment of left-sided large bowel obstruction^{10–12}. It has been suggested that this technique might also be applied in the treatment of patients with acute inflammatory disorders of the left colon^{13,14}. The trend towards resection and anastomosis in selected patients is also supported by recent reviews^{15,16}, but no prospective study of a one-stage

The Editors have satisfied themselves that all authors have contributed significantly to this publication

procedure in the treatment of patients with localized and diffuse peritonitis has been published.

The aims of this prospective study were to evaluate the management of selected patients with left colonic peritonitis using RPA and to compare the results in patients with localized peritonitis with those in patients with generalized peritonitis. The hypothesis was that peritoneal contamination by itself would not increase the anastomotic dehiscence rate, making the one-stage procedure a safe treatment for both localized and diffuse peritonitis in selected patients.

Patients and methods

From January 1994 to December 1998, 127 surgical patients underwent emergency operation, by the same surgical team, for distal colonic perforation. Patients with complicated non-specific inflammatory disease of the colon were excluded. All patients had clinical signs of peritonitis. The indications for surgery and the distribution in surgical groups are given in *Table 1*. Preoperative evaluation of the patients included clinical examination, blood tests, abdominal ultrasonography or computed tomography, and abdominal and chest radiography. ASA grade was recorded for all patients. The relationship between surgical procedure and ASA grade is reported in *Table 2*. All but five patients were operated within 24 h of hospital admission. Three patients with acute diverticulitis, treated with antibiotic parenteral therapy for 3 days, presented with failure of medical treatment and two patients had iatrogenic perforation after renal and gynaecological surgery. All patients were evaluated before operation in an intensive care unit. Renal function and central venous pressure were always monitored. Parenteral antibiotic therapy included prophylaxis against both aerobic and anaerobic bacteria. Antibiotic treatment was continued after operation and changed depending on the type and sensitivity of the organism cultured.

Renal failure was defined as a creatinine level above 1.4 mg/dl, circulatory failure as systolic arterial pressure less than 90 mmHg requiring inotropic support, and respiratory failure as arterial blood oxygenation lower than 60 mmHg.

Immunocompromised status was defined by a concurrent history of exogenous glucocorticoid treatment, extracolonic active malignant neoplasm, cytotoxic chemotherapy, malnutrition, or congenital or acquired immunodeficiency syndrome. Malnutrition was defined as weight loss of more than 10 per cent of normal corporal weight within the preceding 2 months. Immunocompromised status was observed in 18 patients. Only two of these patients with glucocorticoid treatment, one with chronic obstructive pulmonary disease and one with temporal arteritis, were treated by RPA.

The severity of peritonitis was classified according to the staging system of complicated colonic diverticulitis proposed by Hinchey *et al.*¹⁷: stage 1, pericolic abscess (20 patients; 16 per cent); stage 2, pelvic abscess (22 patients; 17 per cent); stage 3, generalized purulent peritonitis (57 patients; 45 per cent); and stage 4, faecal peritonitis (28 patients; 22 per cent).

Reasons for surgery in the local peritonitis group (stage 1 and 2) were failure of medical treatment in three patients, failure of percutaneous drainage in three, misleading diagnosis of appendicitis or gynaecological illness in eight, pneumoperitoneum in nine patients, and persistent clinical signs of diffuse peritonitis or presence of septic status in the remaining patients.

Four types of surgical procedure were used. The first-choice operation was RPA. This was performed in 61 patients (48 per cent) as described previously¹⁸. Exclusion criteria that precluded the use of RPA in 66 patients were faecal peritonitis in 20, preoperative organ failure in 15, immunocompromised status in 16, ASA grade IV in 22 and proximal colon damage in eight. Alternative procedures used were Hartmann's procedure in 55 patients (43 per

Table 1 Indication for surgery and surgical groups

Indication for surgery	RPA	Hartmann procedure	Subtotal colectomy	Colostomy	Total
Diverticulitis	39	32	6	0	77 (61)
Perforated cancer	13	8	1	0	22 (17)
Vascular disorder*	3	9	1	1	14 (11)
Iatrogenic	3	2	0	1	6 (5)
Foreign body	2	2	0	1	5 (4)
Trauma	1	2	0	0	3 (2)
Total	61 (48)	55 (43)	8 (6)	3 (2)	127 (100)

Values in parentheses are percentages. *Ischaemic colitis, perforated groin hernia. RPA, intraoperative colonic lavage with resection and primary anastomosis

Table 2 American Society of Anesthesiologists grade and surgical procedure

	ASA grade				Total
	I	II	III	IV	
RPA	35	21	5	0	61
Hartmann procedure	5	17	15	18	55
Subtotal colectomy	2	2	1	3	8
Colostomy	0	2	0	1	3
Total	42	42	21	22	127

ASA, American Society of Anesthesiologists; RPA, intraoperative colonic lavage with resection and primary anastomosis

cent); subtotal colectomy in eight patients (6 per cent) with associated proximal colonic damage; and colostomy only in three patients (2 per cent) with faecal peritonitis and septic shock, one with ischaemic perforation, one with an iatrogenic endoscopic perforation and one with a perforation secondary to a foreign body.

Both mortality and morbidity rates were analysed in the group of patients treated by RPA, and the results of patients with localized peritonitis were compared with those of patients with generalized peritonitis. Comparison between means was performed using Student's *t* test. Comparison of frequencies was performed by two-tailed Fisher's exact test. $P < 0.05$ was considered significant. Values are mean(s.d.).

Results

Sixty-one patients (31 men and 30 women) were treated by RPA. The mean age was 57(15) (range 22–84) years. Nineteen patients (31 per cent) presented one or more associated major medical problems at the time of operation: chronic obstructive pulmonary disease (eight patients), cardiac disease (three), insulin-dependent diabetes (three), immunocompromised status (two), chronic renal insufficiency (two) and previous malignant neoplasm (one). No patient with ASA grade IV was included in the RPA group (Table 2). Localized peritonitis was observed in 38 patients (62 per cent) and 23 patients (38 per cent) presented with generalized peritonitis. Peritonitis was stage 1 in 17 patients (28 per cent), stage 2 in 21 patients (34 per cent), stage 3 in 21 patients (34 per cent) and stage 4 in two patients (3 per cent). The two patients with stage 4 peritonitis were young (27 and 22 years) and faecal peritonitis was of less than 12 h duration without signs of septic shock.

Two patients (3 per cent), with generalized peritonitis, died. One or more complications were detected in 24

Table 3 Postoperative complications

Complication	No. of patients
Overall	24 (39)
Wound infection	14 (23)
Septic shock	1 (2)
Intra-abdominal abscess	4 (7)
Prolonged ileus	3 (5)
Abdominal wound dehiscence	2 (3)
Pneumonia	2 (3)
Upper gastrointestinal haemorrhage	1 (2)
Anastomotic leakage	1 (2)
Small bowel fistula	1 (2)

Values in parentheses are percentages

Table 4 Comparison of outcome in patients with localized and diffuse peritonitis treated by intraoperative colonic lavage with resection and primary anastomosis

	Localized peritonitis (n=38)	Diffuse peritonitis (n=23)	P
Age (years)*	58(13)	55(18)	0.48†
Complications	15	9	1.00‡
Wound infection	10	4	0.53‡
Reintervention	2	2	0.62‡
Anastomotic leakage	0	1	0.37‡
Deaths	0	2	0.13‡
Hospital stay (days)*	19(18)	16(10)	0.38†

*Values are mean(s.d.). †Student's *t* test; ‡two-tailed Fisher's exact test

patients (39 per cent) treated by RPA (Table 3). Four patients (7 per cent) (two with localized and two with diffuse peritonitis) required reoperation for abdominal wound dehiscence (two), anastomotic dehiscence (one) and intra-abdominal abscess (one). Wound infection occurred in 14 patients (23 per cent). The overall mean hospital stay was 18(15) days.

The outcome of patients with localized and generalized peritonitis is reported in Table 4. No statistical differences were observed between the two groups.

Discussion

There has been debate about the appropriate surgical procedure to be used in colonic perforation. Retrospective studies^{7,19} and a review of published series¹ showed an improvement in survival of patients with peritonitis who underwent resection rather than a conservative procedure. Intraoperative colonic lavage and primary anastomosis has been used successfully to facilitate primary colorectal anastomosis in patients who require urgent resection of

the distal colon to relieve acute mechanical obstruction^{10,13,18,20}. The question that arises is whether a primary anastomosis should be done in the presence of peritonitis, or whether a Hartmann type procedure should be carried out. The classical view is that anastomosis in the presence of peritonitis should be discouraged. Experimentally, Hawley²¹ has shown that faecal soiling or peritoneal sepsis may impair the healing of a colonic anastomosis. Furthermore, a clinical study by Irvin and Goligher²² showed that poor mechanical bowel preparation was associated with a significantly higher incidence of anastomotic dehiscence and suggested that peritoneal sepsis itself did not play a major part in anastomotic dehiscence. Many studies, which reported an increased rate of anastomotic leakage in the presence of abscess or peritonitis, had poor results because of the quality of preoperative mechanical preparation of the colon²³. In 1988, a randomized prospective study by Ravo *et al.*²⁴ concluded that if faeces could be excluded from intraluminal contact with the anastomotic site, an anastomosis may be performed safely even in the presence of peritonitis. Tornqvist *et al.*²⁵ in 1991 failed to confirm, in an animal study, a relationship between peritonitis and anastomotic dehiscence. Other reports^{14,16,26} have recommended construction of a primary anastomosis wherever possible in the presence of peritonitis. Only one of these studies, by Alanis *et al.*¹⁴, recommended this approach in stage 3 peritonitis also. However, this recommendation was based on three patients with diffuse peritonitis without strict patient selection.

In the present series the authors performed RPA in 21 (37 per cent) of 57 patients with generalized purulent peritonitis (stage 3), always following the same exclusion criteria. Ferzoco *et al.*²⁷, in a review of acute diverticulitis, suggested that a two-stage procedure remains the safest option in the presence of peritonitis. However, in a recent report by Elliot *et al.*⁴, seven (14 per cent) of 51 operated patients with perforated diverticulitis were treated by resection and primary anastomosis. In the present study, RPA was performed in 39 (51 per cent) of 77 patients with perforated diverticulitis, with good result. RPA was performed initially only in patients with colonic obstruction and in those with localized peritonitis. However, because of good results²⁸, increasing confidence with the technique and not considering purulent peritonitis to be a formal contraindication for primary anastomosis, RPA was later offered to selected patients with diffuse peritonitis; Hartmann's procedure was therefore performed only in selected patients in poor general condition.

In the authors' experience two patients (3 per cent) in the diffuse peritonitis group died and none in the localized peritonitis group. This is clinically if not statistically significant.

This study shows that about half of the patients admitted with distal large bowel peritonitis may benefit from a one-stage procedure with low morbidity and mortality rates when selected and practised by experienced surgeons, interested in emergency colorectal disease. Generalized peritonitis, age and coexisting medical illness by themselves are not a formal contraindication to resection, perioperative lavage and primary anastomosis. However the presence of septic shock, faecal peritonitis, immunocompromised status or ASA grade IV at admission are considered to be contraindications for the one-stage procedure. In these patients Hartmann's intervention is still considered a valid alternative.

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Ten-year audit of randomized trials in digestive surgery from Europe

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Randomized trials remain scarce in the field of digestive surgical investigation because they present unique features and problems¹. This study was a review of randomized trials in the field of digestive surgery to assess the evolution in Europe over the past decade.

Materials and methods

A comprehensive computerized search was conducted in three databases (Medline, Embase and the Cochrane Library) between 1 January 1990 and 31 December 1999. A manual search was also performed in the past six issues of 14 major journals (*American Journal of Surgery*, *Annals of Surgery*, *Archives of Surgery*, *British Medical Journal*, *British Journal of Surgery*, *Diseases of the Colon and Rectum*, *European Journal of Surgery*, *Gastroenterology*, *Gut*, *Journal of the American College of Surgeons*, *Lancet*, *New England Journal of Medicine*, *Surgical Endoscopy*, *Surgery*). Only original articles comparing two surgical procedures or a surgical and a non-surgical treatment were retained. When the authors were from different countries, the trial was considered as international.

The trials were classified into three categories: category 1, trials evaluating the core procedure itself (similar to drugs); category 2, trials evaluating an important step of the surgical procedure; and category 3, trials evaluating a technical detail.

Results

Two hundred and fifty-one trials were retrieved (approximately two trials published per month). Fig. 1 shows the evolution of the number of trials per year in Europe compared with that in North America, where 52 trials were recorded over the same interval (references for all these trials can be obtained from the author for correspondence). The UK was the country of affiliation in 51 trials (20 per cent of trials), France in 38, Germany in 34, Sweden in 22,

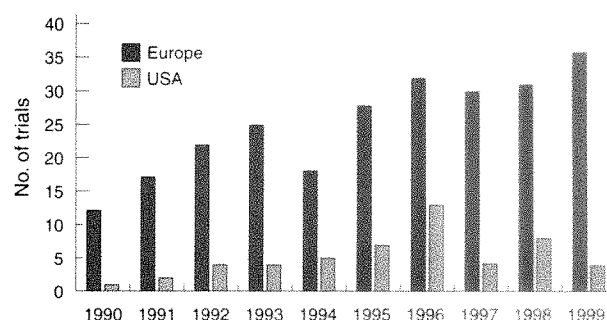


Fig. 1 Evolution of the number of trials per year over the past decade in the field of digestive surgery in Europe and the USA

Table 1 Number of trials (with their category) for each European country and the respective number per million inhabitants

Country	Category			Total no. of trials	No. of trials per million inhabitants
	1	2	3		
UK	20	22	9	51	0.8
France	12	18	8	38	0.7
Germany	14	15	5	34	0.5
Sweden	9	10	3	22	2.8
Finland	2	16	2	20	4.0
Italy	3	13	1	17	0.3
Netherlands	6	6	4	16	1.0
Spain	2	8	4	14	0.4
Denmark	8	3	1	12	2.4
Other	10	13	4	27	0.3
Whole of Europe	86	124	41	251	0.6

Finland in 20 and other countries in 82. There were four international multicentre trials. When the contribution of each country was calculated per million inhabitants, the number of randomized trials was significantly higher in the Nordic countries, namely Finland, Sweden and Denmark (Table 1). Although the number of trials of conventional surgical procedures remained stable (mean about 15 per year), the observed increase was due to trials evaluating laparoscopic procedures (almost half of the published trials over the past 4 years). For the whole of Europe, 210 trials (84 per cent) were in category 1 or 2 (Table 1). In the whole sample, 22 per cent of the trials were multicentre; in France 59 per cent of the trials were multicentre with a range in the other countries from 7 per cent in Spain to 33 per cent in the Netherlands.

Discussion

This study showed that European digestive surgeons design, conduct and publish increasing numbers of randomized trials, mainly since the introduction of laparo-

scopic surgery. Using the approach described it was not possible to ascertain how many trials were incomplete, abandoned or unpublished. In all areas of clinical research there is increasing awareness of the necessity to register all clinical trials to avoid a publication bias². The rarity of multicentre trials should also be addressed since the advantages of multicentre trials are recognized: the broader range of patients and surgeons facilitates the generalization of results and improved national and international collaboration³. The present results also showed how the distribution of trials performed in different countries was heterogeneous. In absolute terms, three countries provided the most: the UK, France and Germany. However, when this was calculated with respect to potential participants, the Nordic countries provided the highest rate of trials. One can speculate about the reasons for these findings. The Nordic countries may be more committed to evaluation than others, or perhaps Nordic patients are more willing to

participate in clinical trials. The apparent increasing enthusiasm of European digestive surgeons should be built upon, and they should be encouraged to perform high-quality randomized (particularly multicentre) trials.

Acknowledgements

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Randomized clinical trials in surgery

The Journal acknowledges the growth in evidence-based surgical practice and wishes to encourage clinical research in surgery. Randomized clinical trials have been awarded priority at the beginning of the Journal. We also review the contents lists of the worlds' top 50 surgical journals; randomized trials identified are featured on the Scientific Surgery page at the back of the Journal. These trials are archived on the *BJS* website (www.bjs.co.uk), where over 300 trials have been collected since the beginning of 1998. If any significant randomized clinical trials have been missed, please let us know and we can add them to the archive. Authors of randomized clinical trials in surgery should remember that they can request fast track publication in the *British Journal of Surgery*.

The Editors

Results of treatment of 33 patients with peritoneal mesothelioma

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Background: Peritoneal mesothelioma is a rare peritoneal malignancy, representing approximately one-third of all mesotheliomas. It is regarded as a universally fatal cancer with few treatment options.

Methods: Records of 33 patients with peritoneal mesothelioma were reviewed retrospectively. Demographic, clinical and quantitative prognostic indicators were evaluated and analysed statistically using survival as endpoint. Patients were treated by a uniform strategy involving cytoreductive surgery with peritonectomy procedures and perioperative intraperitoneal chemotherapy (cisplatin, doxorubicin).

Results: There were ten women and 23 men; mean age was 53.0 years. Asbestos exposure was recorded in five patients and a family history of cancer in 13. Presentation was mainly abdominal distension and pain. Median survival was 31.0 months; overall projected survival at 3 years was 56 per cent. The most significant positive predictive factors of survival were: female sex ($P=0.003$), low prior surgical score ($P=0.002$), completeness of cytoreduction ($P=0.0002$) and second-look surgery ($P=0.019$). The morbidity rate for this combined treatment was 33 per cent and the perioperative mortality rate was 3 per cent.

Conclusions: Although peritoneal mesothelioma is rare, progress in its management has occurred. Survival has been extended and selection factors by which patients may be allocated to aggressive management strategies have been defined.

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Introduction

Mesothelioma is a neoplasm originating from the mesothelial surface lining cells of the serous human body cavities. Mesothelioma may involve the pleura, less frequently the peritoneum and, rarely, the pericardium and the tunica vaginalis testis. Peritoneal mesothelioma is usually a rapidly fatal peritoneal surface malignancy with a median survival of less than 1 year¹. It represents about one-third of all forms of mesothelioma^{1–3}. Several articles have appeared in the medical literature on the asbestos–mesothelioma aetiological link since Wagner *et al.*⁴ first described this important relationship in 1960. Implication of asbestos exposure in the causation of peritoneal mesothelioma is far less obvious than in pleural mesothelioma^{1,5}. This report describes an experience with 33 patients with peritoneal mesothelioma, and analyses their clinicopathological features. Treatment consisted of a combined approach of extensive cytoreduc-

tive surgery with peritonectomy procedures and intraperitoneal perioperative chemotherapy^{6,7}. This aggressive therapeutic approach resulted in successful palliation of ascites and long-term survival was seen in some patients. A search was made for selection factors associated with an improved quality of life and a prolonged survival for patients with peritoneal mesothelioma.

Patients and methods

Patients

The records of 58 patients with primary peritoneal surface malignancy surgically treated between 1989 and 1999 were reviewed retrospectively. Thirty-seven patients with peritoneal mesothelioma were identified together with 13 patients with primary peritoneal adenocarcinoma and eight patients with papillary serous carcinoma of the peritoneum.

This report was restricted to 33 patients with mesothelioma involving exclusively the peritoneum, free from distant metastasis at the time of initial treatment at this institution.

Pathology

Pathological procedures included examination of haematoxylin and eosin-stained sections, routine histochemistry and, when required, specialized immunohistochemical tests for differentiation from other peritoneal surface malignancies. The immunohistochemical stains included: mucicarmine alcian blue, monoclonal antikeratin antibodies CAM5.2 and AE1/3, epithelial membrane antigen, carcinoembryonic antigen (CEA), carcinogenic antigen 125 (CA125), tumour-associated glycoprotein B72.3, monoclonal antibody Ber-EP4, antimyelomonocytic antibody Leu-M1, placental alkaline phosphatase and acid calcium-conjugated S-100 protein.

Clinical features analysed

The following data were retrieved from the patient records and analysed for their impact on survival: age at surgery, sex, race, personal and familial medical history, exposure to asbestos, and use of tobacco and alcohol. From other institutions were gathered date and character of first presenting symptom, date of first diagnosis, previous surgery and adjuvant treatments before referral.

A series of quantitative prognostic indicators for peritoneal surface malignancy was used in an attempt to identify selection factors for treatment: the prior surgical score, the peritoneal cancer index and the completeness of cytoreduction score. All these indicators used survival as an endpoint. The prior surgical score has been described previously⁸ and ranged from zero to 3 (0, no previous surgery; 1, one abdominopelvic region dissected; 2, two to four regions dissected; 3, five or more abdominal regions). The peritoneal cancer index visually assessed the mass of tumour present within the abdomen and pelvis at the time of abdominal exploration. It has also been described previously⁹. It quantified the tumour in 13 abdominopelvic regions by a lesion size score; the size of the largest nodule and not the number of lesions was scored. The lesion size was from zero to 3 (1, lesion smaller than 0.5 cm; 2, lesion smaller than 5 cm; 3, lesion larger than 5 cm or layering of mesothelioma in the region); the maximum peritoneal cancer index was 39 (3 × 13). The completeness of cytoreduction score is another quantitative visual assessment of tumour volume left on the peritoneal surface⁸. In contrast to the peritoneal cancer index, which was scored during abdominal exploration, this scoring occurred after the surgical efforts had been completed. The score ranged

from zero to 3 (0, no tumour; 1, nodules smaller than 0.25 cm; 2, nodules smaller than 2.5 cm; 3, nodules larger than 2.5 cm remaining after surgery or confluent tumour); complete cytoreduction was reflected by a score of 0 or 1. Performance status was assessed using the Zubrod–Eastern Co-operative Oncology Group (ECOG) scale from zero to 5, with zero indicating a normal level of function¹⁰. The following data were recorded from patients' charts and follow-up notes: physical examination and operative findings, surgical procedures, intraoperative and postoperative intraperitoneal chemotherapy treatments, postoperative course and treatments including systemic chemotherapy and radiation, second- and third-look operative procedures, tumour marker levels, presence or absence of metastasis, survival status, date and cause of death.

Treatments

The goal of the treatment was to use both surgery and regional chemotherapy maximally in every patient, to the limits of patient tolerance¹¹. Nine patients with extensive ascites were treated before surgery with induction intraperitoneal chemotherapy using cisplatin (Platinol; Bristol Myers Squibb Company, Pennington, New Jersey, USA) at 15 mg per m² per day and doxorubicin (Adriamycin; Ben Venue Laboratories, Bedford, Ohio, USA) at 6 mg per m² per day. Each cycle of treatment was for 5 consecutive days, given once a month for 3 months. After the induction intraperitoneal chemotherapy the patients went on to cytoreductive surgery. The other 24 patients' initial treatment at this institution was cytoreductive surgery, which included all or part of the following five peritonectomy procedures, which have been described previously: greater and lesser omentectomy, right and left subphrenic peritonectomy and complete pelvic peritonectomy⁶. Visceral resections were often required for complete cytoreduction. During the surgical procedure the patients had intraoperative intraperitoneal chemotherapy with cisplatin 50 mg/m² and doxorubicin 15 mg/m², heated to 41–41.5°C¹². Patients who had a moderate-to-large volume of mesothelioma left behind after surgery were treated with additional cycles of postoperative intraperitoneal chemotherapy, with a similar dose and schedule to the induction treatment. Toxicity was recorded and graded according to the National Cancer Institute Common Toxicity Criteria¹³. Follow-up was updated until 15 August 1999.

Statistical analysis

Survival was retained as endpoint for all statistical analysis, and was determined from the time of initial diagnosis. The

survival curves were obtained using the Kaplan–Meier method and comparison of survival was by log rank test^{14,15}. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Demographic and epidemiological data

The significant data are summarized in *Table 1*. The mean age was 53.0 (range 17–79) years. There was a statistically significant advantage in survival for women: median 41 *versus* 16 months for men ($P = 0.003$). Thirty-one patients were Caucasian; there was one African American and one Asian American. Twelve patients had no history of exposure to asbestos, five had a positive history (two worked in a shipyard, one in a cement factory, one with insulation and one as an electrician) and there were no data on 16 patients. Six patients were tobacco users. The alcohol consumption rate was low (four patients) and no patient used recreational drugs. Thirteen patients had a family history of cancer (in a parent or sibling), five of whom had more than one first-degree relative with a malignancy.

Symptoms, signs and diagnosis

The commonest initial complaints for peritoneal mesothelioma, isolated or combined, were an increasing abdominal girth (22 patients), abdominal pain (nine) and weight loss (six). Ascites was present at time of diagnosis in 22 patients and was debilitating in six (*Table 1*). Unusual presentations included acute abdomen (one) and rectal bleeding (one). The mean interval from onset of symptoms to diagnosis was 5 (range 0–33) months. The mean interval from diagnosis to definitive cytoreduction was 9 (range 1–48) months. Diagnosis of peritoneal mesothelioma was made by laparotomy in 18 patients, by laparoscopy in ten, and by abdominal puncture and cytology in five patients.

Treatments before definitive cytoreduction and intraperitoneal chemotherapy

Sixteen patients received chemotherapy before cytoreductive surgery: intraperitoneal (nine), systemic (seven) and both (two). These chemotherapy treatments before and after cytoreductive surgery were not part of a systematic perioperative approach, but reported as treatments received at different institutions. No patient underwent irradiation. Induction intraperitoneal chemotherapy was successful in eight of nine patients but there was no significant impact on survival (*Table 1*). The performance status before cytoreduction was zero or 1 in 21 patients and 2–4 in 12 patients; their median survival was 29 and 17 months respectively

Table 1 Significant epidemiological and clinical data on 33 patients with peritoneal mesothelioma

	No. of patients	Median survival (months)	P*
Age (years)			0.21
≤ 53	16	28	
> 53	17	17	
Sex			0.003
Female	10	41	
Male	23	16	
Asbestos exposure			0.49
Yes	5	15	
No	12	16	
Unknown	16	33	
Ascites			0.61
Yes	22	17	
No	11	34	
Debilitating	6	26	
Preop. chemotherapy			0.55
Systemic	7	34	
Intraperitoneal	9	35	
Both	2	51	
Performance status			0.03
0–1	21	29	
2–4	12	17	
Prior surgical score			0.002
0	18	41	
1–3	15	16	

Survival was measured from the time of diagnosis. *Log rank test

($P = 0.029$). The prior surgical score was zero in 18 patients and 1–3 in 15 patients; the median survival was 41 and 16 months respectively ($P = 0.002$) (*Table 1*).

Treatment data

Significant data regarding treatments are shown in *Table 2*. Between 1989 and 1999, 47 cytoreductive procedures were performed on 33 patients with peritoneal mesothelioma by the same surgeon: 33 as a first procedure, 11 as second-look and three as third-look surgery. Twenty of the 33 patients had the first cytoreduction after 1995. Twenty patients received a major first cytoreduction involving four or more abdominopelvic regions. Thirteen patients, with high comorbidity or irresectable peritoneal mesothelioma, had a less extensive debulking procedure; a comparison of survival approached statistical significance in favour of major cytoreduction ($P = 0.07$). Mean operating time was 6.8 (range 2–13.5) h; mean ascites volume was 2.4 (range 0–14) litres; mean blood requirement was 2 (range 0–8) units. For the initial 33 cytoreductions the mean peritoneal cancer index was 29. For patients with a score of 0–28 the median survival was 34 months compared with only 16 months for patients with a score between 29 and 39;

Table 2 Significant treatment data on 33 patients with peritoneal mesothelioma

	No. of patients	Median survival (months)	P*
Cytoreduction			0.07
Major	20	38	
Minor	13	15	
Peritoneal cancer index			0.026
0–28	17	34	
29–39	16	16	
Completeness of cytoreduction score			0.0002
0–2	17	41	
3	16	13	
Periop. intraperitoneal chemotherapy			0.11
Yes	28	28	
No	5	18	
Second-look surgery			0.019
Yes	11	35	
No	22	16	
Metastasis			0.001
Yes	7	17	
No	21	29	
Unknown	5	11	
Status			
No evidence of disease	8	38	
Alive with disease	10	23	
Dead from disease	15	16	

Survival was measured from the time of diagnosis. *Log rank test

the peritoneal cancer index was a statistically significant predictor of survival ($P=0.026$). The completeness of cytoreduction score was 0–2 in 17 patients and 3 in 16 patients, with a median survival of 41 and 13 months respectively ($P=0.0002$). Twenty-eight patients received perioperative intraperitoneal chemotherapy (heated intra-operative treatment, postoperative treatment or both) and five patients did not; their median survival was 28 and 18 months respectively ($P=0.11$). Eleven patients had a scheduled second-look cytoreduction 6–9 months after the first operation, combined with perioperative intraperitoneal chemotherapy in ten. Three patients had a third-look operation. Median survival was 35 months in the 11 patients who had second-look surgery compared with 16 months in the other 22 patients; this was statistically significant ($P=0.002$), although the survival advantage may have resulted from selection factors inherent to that group of patients.

Morbidity and mortality

There were 11 patients with grade III–IV complications, giving an overall morbidity rate of 33 per cent. Four patients

Table 3 Pathology of peritoneal mesothelioma

	No. of patients	No evidence of disease	Alive with disease	Dead from disease
Multicystic	2	2	0	0
Adenomatoid multicentric	1	1	0	0
Epithelial				
Epithelioid	10	2	3	5
Tubulopapillary	17	3	7	7
Biphasic	2	0	0	2
Sarcomatous	1	0	0	1
Total	33	8	10	15

required reoperation for persistent bile leak from the liver surface (one), small bowel fistula (one) and late intra-abdominal bleeding (two). There was one perioperative death from sepsis that occurred 33 days after surgery.

Pathological features

Thirty-three patients retained a diagnosis of peritoneal mesothelioma (Table 3): 30 malignant, two low-grade malignant multicystic mesotheliomas and one multicentric aggressive adenomatoid mesothelioma. The malignant mesothelioma subtypes were epithelial in 27 patients, subdivided into ten epithelioid and 17 tubulopapillary lesions, biphasic or mixed in two patients and sarcomatous in one. All three patients with mesothelioma of low malignant potential are free from disease; the three patients with an aggressive subtype have died from the disease, and patients with epithelial histology showed a mixed response to treatment.

Follow-up and survival

The median follow-up after cytoreduction was 21.3 (range 1–79) months. No patient was lost to follow-up. During follow-up distant metastases were later diagnosed in seven patients: liver (one), mediastinum (one), lung (two) and pleural cavity (three). All patients who developed distant metastasis have died from the disease. Twenty-one patients had no metastasis and there were no data on five patients (Table 2). The occurrence of metastasis decreased survival significantly ($P=0.001$).

Fifteen patients died from the disease and 18 patients are still alive (Table 2). Ten are alive with disease and eight have no evidence of disease by imaging, tumour markers and second- or third-look surgery. The median survival from diagnosis was 31.0 months. The Kaplan–Meier survival curve for this group is shown in Fig. 1. The projected overall survival at 1, 3 and 5 years is 77, 56 and 47 per cent respectively.

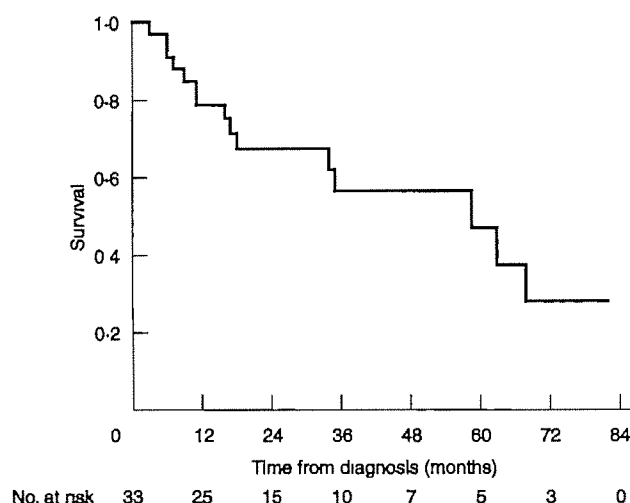


Fig. 1 Kaplan-Meier survival curve of 33 patients with peritoneal mesothelioma. Median survival from diagnosis was 31.0 months

Discussion

Peritoneal mesothelioma has evolved over almost 100 years from a clinical oddity to an established rare disease of increasing importance. In 1908 Miller and Wynn¹⁶ first described '...a malignant tumour arising from the endothelium of the peritoneum and producing mucoid ascitic fluid.' In 1909 Adami¹⁷ first used the term mesothelioma to refer to a highly malignant tumour of the serosal membranes involving mostly the pleura and the peritoneum, and less often the pericardium and tunica vaginalis testis. Mesothelioma is not specific to humans and is also found in other mammalian species, including horse, monkey, dog and cow¹⁸⁻²⁰. The link between mesothelioma and exposure to asbestos is widely accepted; its incidence is increasing in the industrialized nations^{21,22}. Peritoneal mesothelioma represents 20-37 per cent of all mesotheliomas¹⁻³; because of its rarity and the small size of published series, an estimation can only be made of 200-400 new cases annually in the USA. Four histological types of malignant peritoneal mesothelioma are recognized: epithelial (75 per cent), sarcomatous, mixed or biphasic and poorly differentiated; multicystic and multicentric adenomatoid peritoneal mesothelioma has a malignant potential²³⁻²⁵.

In a review of the literature no dominant therapeutic guideline for peritoneal mesothelioma was found. Few articles were clinicopathological retrospective reviews and most were case reports compiling disparate and deceptive therapeutic experiences, including use of systemic chemotherapy, whole abdomen irradiation, and intraperitoneal treatments with compounds such as colloidal radioactive

³²P and ¹⁹⁸Au, thiotepa and bleomycin^{3,26,27}. More recent reports show a more systematic approach to peritoneal mesothelioma, with debulking surgery and systemic chemotherapy with paclitaxel, cisplatin alone or doxorubicin²⁸⁻³⁰. A phase I trial with 18 patients reported a similar approach to the present one, with promising preliminary results³¹. The prognosis is grim after diagnosis of peritoneal mesothelioma: survival of 7-13.5 months and only a few long-term survivors are reported^{1,3,26,32,33}. The median survival in this group was 31.0 months from diagnosis, with a projected 3-year survival of 56 per cent. These results need to be tempered by the relatively short follow-up after cytoreduction.

In this study, positive predictive factors of survival were identified by univariate analysis: (1) female sex (2), good health status, (3) minimal previous surgery, (4) low peritoneal cancer index, (5) low completeness of cytoreduction score and (6) second-look surgery (for selected patients); these factors correlated with improved survival. There was a suggestion that partial debulking or resection of mesothelioma in the absence of intraperitoneal chemotherapy may jeopardize subsequent treatment. Patients who had a high prior surgical score were not as likely to survive long term. The peritoneal surface malignancy may be moved more rapidly to an invasive process if anatomical defences are destroyed by surgery. In patients who had trocar-site tumour progression, the abdominal wall masses progressed more rapidly than residual tumour in the abdomen.

Patients in whom major resection of the mesothelioma was possible, reflected by a low completeness of cytoreduction score, survived statistically longer. Patients with minimal or no progression of disease and no systemic component of mesothelioma were candidates for a second-look reoperation. In this selected group the survival was significantly prolonged. These findings suggest, but do not confirm, that aggressive cytoreductive surgery is of value in this group of patients and should be recommended.

There was no statistical indication that intraperitoneal chemotherapy resulted in survival benefit. It is possible that selection factors were important in this evaluation, because patients with a large volume of mesothelioma after cytoreduction were usually not given intraperitoneal chemotherapy. However, it may be unwise to conclude that intraperitoneal chemotherapy may be eliminated from the treatment regimen. Compared with previous experience with this disease, the benefits of intraperitoneal chemotherapy in palliation were thought to be substantial. All but one patient had no further symptoms from ascites after cytoreduction and perioperative intraperitoneal chemotherapy. In the group of patients with resection of gross disease (completeness of cytoreduction score 1 or 2)

intraperitoneal chemotherapy may have been an essential component of the treatment that resulted in long-term survival. With the current state of knowledge, a recommendation for intraperitoneal cisplatin and doxorubicin as a standard treatment for peritoneal mesothelioma, combined with cytoreductive surgery, may be worthy of consideration.

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Correspondence

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Barrett's oesophagus — 50 years on

Sir

We read with interest the recent leading article on Barrett's oesophagus (*Br J Surg* 2000; 87: 529–31) which provides an informative overview on the natural history and management of this condition. Barrett's oesophagus confers significant increased risk of oesophageal adenocarcinoma and treatment is therefore naturally focused towards reducing the risk of progression to malignant disease. One factor worthy of consideration in this regard, but largely ignored to date, is obesity. Increases in the prevalence of obesity correlate strongly with the rise in oesophageal adenocarcinoma incidence over recent decades and a significant positive association between the two has now been reported by at least four case-control studies¹. A plausible mechanism links obesity and increased intra-abdominal pressures² with gastro-oesophageal reflux disease³ and increased risk of oesophageal adenocarcinoma. A significant beneficial effect of weight loss on symptoms of gastro-oesophageal reflux in overweight patients has already been demonstrated⁴. If this is an important risk factor for oesophageal adenocarcinoma and Barrett's oesophagus is an intermediate step on the causal pathway to malignant disease, then the role of obesity in the management of Barrett's oesophagus clearly warrants further investigation.

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- 1 Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the oesophagus and gastric cardia. *Ann Intern Med* 1999; 130: 883–90.
- 2 Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity co-morbidity. *J Int Med* 1997; 241: 71–9.
- 3 Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Risk factors associated with symptoms of gastro-oesophageal reflux. *Am J Med* 1999; 106: 642–9.
- 4 Fraser-Moodie CA, Norton B, Gornal C, Magnago S, Weale AR, Holmes GKT. Weight loss has an independent effect on symptoms of gastro-oesophageal reflux in patients who are overweight. *Scand J Gastroenterol* 1999; 34: 337–40.

Role of relaparoscopy in the management of minor bile leakage after laparoscopic cholecystectomy

Sir

I read with interest the article by Wills *et al.* (*Br J Surg* 2000; 87: 176–80) and I would agree that laparoscopy is useful in the management of minor biliary leakage.

I would like to comment on two points. Firstly, if the natural history of a well-drained minor biliary leak from a perivesical duct is spontaneous resolution¹ how can the authors assume that the addition of duct suturing hastens recovery? The study structure and patient numbers do not allow this question to be answered.

Secondly, if patients with major biliary leakage were excluded from the study how can the authors conclude that these cases are not suitable for laparoscopic management?

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- 1 McQuillan T, Manolas SG, Hayman JA, Kune GA. Surgical significance of the bile duct of Luschka. *Br J Surg* 1989; 76: 696–8.

Author's reply

Sir

It needs to be appreciated that data from the prelaparoscopy era is not necessarily relevant to the management of complications after laparoscopic cholecystectomy. We know from observations made at repeat laparoscopy that adhesion formation around the gallbladder bed is much less extensive after laparoscopic cholecystectomy. Further, if a T-tube inserted at laparoscopy is removed at 10 days, as was the custom with open surgery, then there is a high risk of bile leakage due to failure of adhesions sealing off the leak. In the data presented in our paper, there were several instances where drains failed to achieve control because there was a failure of the omentum to seal either the leak or to establish a controlled fistula.

Major leaks were not the subject of our paper but our concern with going straight to laparoscopy for control is that, until we have imaging of the biliary tree, usually by ERCP, we cannot exclude a transection injury.

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Bacterial translocation in patients undergoing abdominal aortic aneurysm repair

Sir

On the basis of a single case, Woodcock *et al.* (*Br J Surg* 2000; 87: 439–42) speculate that graft infection might be accounted for by bacterial translocation. Their hypothesis is weakened by the incomplete identification of the organism. The thrust of their paper is that bacterial translocation is associated with septic complications but we are not told what specific infections

were recorded in the three patients in whom the same organism was grown from both the mesenteric lymph node and the infected site. Yet, of the 16 septic complications reported in the study, eight were chest infections, four urine infections and one a wound infection. These are not uncommon after major abdominal surgery and their pathogenesis is sufficiently understood. Are the authors suggesting that infection at these sites could be caused by bacterial translocation? The case for a causal link between bacterial translocation and mortality is compelling in the laboratory rat. In contrast clinical studies have yielded, at best, weak evidence of a relation between bacterial translocation and septic morbidity. One might speculate that it is epiphenomenal rather than causal.

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Letter 2

Sir

The paper by Woodcock *et al.* (*Br J Surg* 2000; 87: 439–42) requires comment. It is commonly accepted that prophylactic antibiotics should be given 30 minutes before skin incision, or certainly no later than with the induction of anaesthesia¹. The results of this study appear flawed because of the delay until after lymph node excision. In order to validate the reported outcome the authors need a comparable series of patients having the same bacteriological investigation, but having had their antibiotics prophylactically administered at the usual time prior to commencing surgery. If results were the same their claim of bacterial translocation and its potential significance would be supported. If not it might be further evidence of the importance of the timing of administration of prophylactic antibiotics in this situation.

The question of bacterial growth from the serosal exudate of the intestines placed in a polythene bag – a practice by no means universally followed and a situation where the intestine is in an abnormal milieu for three to four hours – raises the possibility that this manoeuvre is responsible for any positive bacterial cultures.

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- 1 Antimicrobial prophylaxis in surgery. *Med Lett Drugs Ther* 1999; 41: 75–9.

Author's reply

Sir

I am grateful to Dr Saadia and Professor Singer for their interest in our paper. Our conclusion from this observational study was simply that bacterial translocation occurs in patients undergoing surgery for abdominal aortic aneurysm and that it

is associated with an increased incidence of postoperative septic morbidity. It is interesting to speculate that one possible cause of late graft sepsis might be bacterial translocation. The clinical implications of this and its relevance to antibiotic prophylaxis are obvious.

Our study was based on a review of 51 patients, five of whom had evidence of bacterial translocation confirmed. Three patients grew the same organism in the mesenteric lymph node at the time of surgery and from a postoperative septic focus. This evidence and that from previous work does support the hypothesis that infection at distant sites from the gut such as chest, urine or wound can be caused by bacteria originating from within the gut¹. We concur with Dr Saadia's view that typing of organisms would be necessary to confirm this but there are practical difficulties and the costs involved are significant.

Professor Singer suggests that our results might be flawed because of the delay in administering prophylactic antibiotics until after lymph node excision. I agree that the timing of administration of prophylactic antibiotics is important and this might have influenced the point prevalence of bacterial translocation. I decided to administer antibiotics after lymph node excision as this adheres to the strict research protocol that we have followed ever since we embarked upon studies investigating bacterial translocation. Not to have had consistency in these results would seem inappropriate. The Local Research Ethics Committee approval has been given for this practice. This study, as well as others, showed no evidence of increased septic morbidity by marginal delay in the administration of antibiotics. To give antibiotics on induction of anaesthesia means that they are being administered 20 minutes before they would be given at lymph node excision. Professor Singer may feel that this slight delay in the administration of antibiotics is clinically relevant but in view of the above I think it improbable.

The use of a bowel bag during aneurysm surgery was the original stimulus for this study. On completion of aneurysmectomy it was common to see large amounts of fluid within these bags and I wondered whether or not this might be teeming with organisms. As the results from this observational study show, this is not the case. This might reflect the fact that the contents of the small bowel are usually sterile and that high concentrations of organisms only occur in the terminal ileum and colon. It is therefore for individual surgeons to decide whether or not the unproven risk of contamination from serosal fluid is offset by perceived advantages in operative exposure.

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- 1 MacFie J, O'Boyle CJ, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora and septic morbidity. *GUT* 1999; 45: 223–8.

Intraoperative sentinel lymph node examination by imprint cytology and frozen sectioning during breast surgery

Sir

The article by Motomura *et al.* (*Br J Surg* 2000; 87: 597–601) raises one or two issues. It is theoretically possible to detect all tumour cells by imprint cytology (IC) when conventional sectioning of the sentinel nodes is negative by haematoxylin and eosin (HE) staining of the embedded material (seven patients; 22 per cent of positive cases). The possibility of false-positive cytology exists. Accepting the true-positive IC results of these seven patients, the significance of these 'positivities' remains to be clarified. A micrometastasis should be terminologically differentiated from isolated tumour cells of unknown character which may or may not progress to micrometastases. Examples of isolated tumour cells, as defined by the UICC¹, are depicted in Figure 1b and c. The incorporation of isolated tumour cells, micrometastases and macrometastases within the single sentinel node-positive category will probably confuse the results of ongoing sentinel node trials and will increase the probabilities of the stage migration artefact². It would be wise to distinguish between subcategories of nodal involvement in all future trials evaluating sentinel node biopsy in patients with breast cancer.

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- 1 Hermanek P, Hutter RVP, Sobin LH, Wittelkind C. Classification of isolated tumour cells and micrometastasis. *Cancer* 1999; 86: 2668–73.
- 2 Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; 312: 1604–8.

Author's reply

Sir

The main purpose of our study was to develop a new means of examining the sentinel lymph node status with more accuracy than frozen section. It was not to study the biological significance of micrometastases and isolated tumour cells in lymph nodes. We could demonstrate that imprint cytology was a significantly better method than frozen section in the diagnosis of positive sentinel lymph nodes. In this study micrometastases were regarded as positive and isolated tumour cells were regarded as negative since the bulk of evidence has suggested, though not completely proven, that only micrometastases can serve as a significant prognostic factor¹.

We agree with Dr Cserni's comment that lymph node metastases should be divided into three categories (macrometastases, micrometastases, and isolated tumour cells)

and analysed separately in future studies because the biological significance of these metastases can be different. This important issue needs to be examined in detail in future studies.

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- 1 International (Ludwig) Breast Cancer Study Group. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. *Lancet* 1990; 335: 1565–8

Fournier's gangrene: a review of 1726 cases

Sir

This review article (*Br J Surg* 2000; 87: 718–28) made interesting reading. Fournier's gangrene is indeed a perplexing problem to treat with potentially fatal results and seems to be more common in developing countries. It is not uncommon in southern India and presents with extensive damage of tissues and morbidity of frightening proportions. This may be due to the late presentation of patients due to relative inaccessibility to hospital care and the economic burden of taking time off work to seek medical attention. One wonders whether early institution of antibiotic therapy would make a dramatic impact in reducing morbidity and mortality.

Two patients that presented to my unit while working in a large district general hospital were postoperative complications (one following a hernia repair and the other following a Hartmann's procedure). Three patients presented *de novo* without any antecedent cause or injury. A special management problem is the preservation of the testes in these relatively young patients and I note the author's point about the occasional need for orchidectomy. In two patients, despite a grossly necrotic scrotum and perineum which had to be extensively debrided, the testes could be implanted in a pouch created in the relatively well-preserved tissues of the thigh. Another patient with exposed testes was managed by means of nonadherent dressings with regular irrigation of saline to prevent drying out until such time as the infection resolved and cover could be achieved. Once the infection cleared up the patients made a remarkable recovery with regeneration of the scrotum and perineum. Perhaps these patients have a greater resistance to fulminating organisms or the organisms are less virulent than those seen in the western world.

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Surgical Anatomy and Technique Pocket Manual. 2nd Ed.

J. E. Skandalakis, P. N. Skandalakis, L. J. Skandalakis
203 × 133 mm. Pp 718. Illustrated 2000 New York Springer £26.50.

This book hopes to marry anatomy with surgical procedures. There are many good black and white line drawings and illustrations taken from other anatomical texts. The surgical procedures that it studies have a North American flavour and a bias towards laparoscopic techniques. The preface to this American 'pocket text' suggests that surgical residents are ill-prepared for training in the operating theatre because of a lack of basic surgical anatomy knowledge. The text is designed to be used by junior residents or medical students but it is not light; carrying this text around in a pocket on a regular basis is probably impractical. Examining three common surgical techniques in detail, some deficiencies are apparent. Simple mastectomy is not described and axillary lymph node groups are well-illustrated in anatomical terms but not related to surgical dissection levels 1-4. A confusing array of inguinal hernia repairs are described. There are long descriptions of the laparoscopic hernia repair and other less common repairs but there is only a short description of the now prevalent on-lay mesh repair (with no diagram). The Shouldice repair, dear to anatomists' hearts, is described in great detail. Carotid endarterectomy, an operation which reveals many anatomical features, is not described (nor is any other vascular operation).

The writing in this text is clear and concise. The line diagrams are helpful and illustrate the text well. While the text deals with the modern application of laparoscopic procedures it falls down by not incorporating current trends in surgery. Many UK trainees, I suspect, would still find a combination of a colour anatomy atlas and an operative surgical text more useful.

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Management of Prostate Cancer

E. A. Klein (ed)
260 × 182 mm Pp. 372 Illustrated. 2000 Totowa, New Jersey Humana Press \$125 00

At a time when prostate cancer is highly topical and its incidence in the UK rising due to better public awareness, this book (as the title suggests) offers a comprehensive and up-to-date review on aspects of screening for the detection of organ confined disease, clinical management of disease at different stages and surgical techniques. Novel areas of investigation and treatment are also covered, based on antibody technology and gene-directed therapy. The authors are exclusively based in the USA, mainly at the Cleveland Clinic Foundation; each chapter provides a balanced and unbiased account, particularly so on issues of controversy and uncertainty, such as screening for prostate cancer, and choice of treatment with watchful waiting or radiotherapy. The chapters on molecular genetics, markers of progression and gene therapy are well-written and would be easily followed by those without an extensive background in molecular and cell biology techniques. For those readers who subspecialize in prostate cancer, the chapters on locally advanced disease, recurrent disease after definitive therapy, management of hormone refractory disease and counselling patients will be of help to their clinical practice. In summary, this book is both timely and useful for all clinicians who wish to obtain a clear and up-to-date account of the management of prostate cancer.

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Scientific Surgery

Sykes TCF, Brookes P, Hickey NC. A prospective randomised trial of tourniquet in varicose vein surgery. *Ann R Coll Surg Engl* 2000; **82**: 280–2.

Use of the Lofquist cuff reduced blood loss, duration of operation and postoperative bruising, but had no effect on postoperative pain, activity scores or cosmetic results in this trial including 50 patients

Liu ST, Wu CT, Yeh CC, Ho ST, Wong CS, Jao SW *et al.*

Premedication with dextromethorphan provides posthemorrhoidectomy pain relief. *Dis Colon Rectum* 2000; **43**: 507–10. Pre-emptive analgesia reduced the need for postoperative pethidine and improved pain scores in the 60 patients studied.

Naver LPS, Gottrup F. Incidence of glove perforations in gastrointestinal surgery and the protective effect of double gloves: a prospective, randomised controlled study. *Eur J Surg* 2000; **166**: 293–5.

Double gloving reduced the rate of hand contamination from 13 to 2 per cent ($P < 0.005$) in this study of 566 pairs of gloves.

Rossle M, Ochs A, Gulberg V, Siegerstetter V, Holl J, Deibert P *et al.* A comparison of paracentesis and transjugular intrahepatic portasystemic shunting in patients with ascites. *N Engl J Med* 2000; **342**: 1701–7.

Sixty patients with ascites due to cirrhosis were included. Survival without the need for liver transplantation was significantly improved in patients who had portasystemic shunting

Rice DC, Morris SM, Sarr MG, Farnell MB, van Heerden JA, Grant CS *et al.* Intraoperative topical tetracycline sclerotherapy following mastectomy: a prospective randomized trial. *J Surg Oncol* 2000; **73**: 224–7.

Postoperative results were similar, but tetracycline actually increased the number of seromas identified two weeks after surgery in this study including 62 patients.

Konsten J, Baeten CGMI. Hemorrhoidectomy *versus* Lord's method: 17 year follow-up of a prospective randomized trial. *Dis Colon Rectum* 2000; **43**: 503–6.

Late follow-up included 118 of 138 patients originally randomized to either hemorrhoidectomy, or anal dilatation with, or without postoperative dilators. Hemorrhoidectomy had the lowest recurrence rate (26 *versus* 46 and 39 per cent, respectively). Various disorders of continence were found in 52 per cent of patients who had an anal stretch

Whelan TJ, Levine M, Julian J, Kirkbride P, Skingley P. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. *Cancer* 2000; **88**: 2260–6.

Some 837 women with axillary node negative breast cancer who had breast conserving therapy were randomly allocated to radiotherapy or control groups. Radiotherapy affected quality of life during treatment but two years later the two groups were similar.

Violi F, Marubini E, Coccheri S, Nenci GG. Improvement of walking distance by defibrotide in patients with intermittent claudication – results of a randomized placebo-controlled study. *Thromb Haemostas* 2000; **83**: 672–7.

Some 310 patients were randomly allocated placebo or one of two different doses of defibrotide. Up to 90 days, results were similar, but by one year defibrotide had significantly improved the absolute walking distance ($P < 0.01$)

Lorenz D, Starke E, Oestreich K, Richter A. Laparoscopic hernioplasty *versus* conventional hernioplasty (Shouldice): results of a prospective randomized trial. *World J Surg* 2000; **24**: 739–45.

Some 176 patients were enrolled in this study evaluating transabdominal preperitoneal hernia repair (TAPP). Two-year recurrence rates were similar but patients who had TAPP had less postoperative pain, shorter hospitalization and quicker return to work.

Hsiao W-C, Young K-C, Wang S-T, Lin P-W. Incisional hernia after laparotomy: prospective randomized comparison between early-absorbable and late-absorbable suture materials. *World J Surg* 2000; **24**: 747–51.

The trial compared polyglactin (early) and polydioxanone (late-absorbable) sutures in 340 patients. There was no difference in the rate of incisional hernias in patients having surgery for non-malignant diseases between the groups, but the rate was lower using polydioxanone in patients with malignant disease (0 *versus* 4.7 per cent)

Selvaggi F, Guiliani A, Gallo C, Signoriello G, Riegler G, Canonico S. Randomized controlled trial to compare the J-pouch and W-pouch configurations for ulcerative colitis in the maturation period. *Dis Colon Rectum* 2000; **43**: 615–20.

Twenty-four patients were randomized and followed for 12 months after ileostomy closure. Functional results (maximum tolerated volume, use of medication, night defaecation) were better with a W-pouch.

Miettinen RP, Pekka J, Laitinen ST, Makela JT, Paakkonen ME. Bowel preparation with oral polyethylene glycol electrolyte solution *versus* no preparation in elective open colorectal surgery: prospective randomized study. *Dis Colon Rectum* 2000; **43**: 669–74.

None of the 267 patients included died postoperatively and median hospital stay was eight days in both groups. There were no differences in any outcome measures such as anastomotic leaks (4 per cent after bowel preparation *versus* 2 per cent in controls) or wound infection (6 *versus* 5 per cent, respectively).

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparsely*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension

Abbreviations must be used consistently and must be defined on first use

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Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript:¹ or ^{1–3}. References cited only in tables or figures should be numbered in sequence.

Non-intervention and palliative care in vascular patients

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Our technical ability to offer operative treatment to patients with peripheral arterial disease is now almost limitless. The development of modern surgical techniques has been paralleled by advances in both anaesthesia and interventional radiology. The inclination to offer intervention is strong: by their nature surgeons want to 'do something' to help the patient, and they like doing operations. In many parts of the world there are powerful financial motives, and the expectations of patients and their families for intervention may also be an important influence. However, surgical enthusiasm should always be tempered by careful consideration of what is really best for the patient; an immediate embrace of what is technically possible may not be wise in all circumstances. Elderly patients with arterial disease pose special dilemmas in deciding when to opt for conservative treatment rather than intervention, particularly patients with aortic aneurysms (both elective and leaking) and those with limb ischaemia.

We now know that the risks of repairing small aortic aneurysms (less than 5.5 cm in diameter) generally outweigh the benefits¹, but we have imperfect knowledge of the risk to the individual of rupture of larger aneurysms. It is conventional wisdom to offer surgery for aneurysms of 5.5–6.0 cm diameter or wider, but at around 6.0 cm the 2-year mortality rate from rupture is well under 50 per cent, and many patients with larger aneurysms survive for years to die from an unrelated condition². These are important considerations for patients with serious comorbidities, which both increase the risk of perioperative death and also limit life expectancy. For the very elderly, aortic surgery is a major blow to function and well-being in the short term, and the patient's own preference about operative or non-operative management (after explicit counselling) should be an important aspect of any decision. The availability of endovascular stent grafts may affect the decision-making process, but it also introduces a new set of dilemmas.

When aortic aneurysms present with leakage or rupture the considerations are rather different because without operation patients will die. Nevertheless, almost all vascular surgeons advise against operation in a proportion of patients, especially those who are very old, who have advanced neurological disease or multiple comorbidities, and who present with features known to militate against survival (for example cardiac arrest, loss of consciousness, prolonged hypotension)³. Two major problems are the

frequent absence of medical information about patients in the emergency setting and the lack of really reliable predictive factors. Chance of survival should not be the sole arbiter of these difficult decisions; the existence of close caring relatives, the possibility of a fulfilling and happy social future and cost effective use of resources all need to be taken into account.

Limb ischaemia involves a wide range of decisions about intervention or conservative treatment. For claudicants the fundamental management is advice and control of risk factors, and there is now evidence of the efficacy of exercise training. By contrast, infrainguinal balloon angioplasty, bypass grafting and thrombolysis (for acute-onset claudication) all carry significant risks of failure in the short and medium term^{4–6}, so patients need to be advised and selected very carefully. Uncorrected risk factors (for example smoking), modest symptoms, other limiting disabilities, more distal disease, and similar symptoms in the opposite leg should all argue against intervention.

Decisions about revascularization in more severe ischaemia may be far from straightforward. Can the patient stand or walk, and if not, why not? Is rest pain disturbing sleep and how much analgesia is needed? Is harmless dry gangrene of one toe present or is there spreading, smelly infection? Is the patient independent or in a nursing home? All of these factors may influence treatment decisions, because they determine both the amount of benefit that might be obtained and also the urgency of any intervention. Many elderly, compromised patients are more kindly treated expectantly, rather than opting for early operative intervention, especially if a high-risk distal bypass is required (for example using a narrow-calibre saphenous vein into a poor distal artery or in the presence of bad occlusive disease of the foot arteries). Others face a lower risk and a better chance of rehabilitation with primary amputation⁷, rather than undergoing a reconstruction which looks likely to fail or which offers a poor prospect of ambulation and quality of life⁸.

Finally, there is a group of patients who present with unsalvageable ischaemia but who have a negligible chance of survival or any quality of life after amputation. The most humanitarian decision is then to opt for good terminal care⁹. Patients with advanced or neglected acute ischaemia in particular may be best treated by analgesia and palliative measures, for example when it is clear that acute limb ischaemia is just one part of a terminal illness or when a

patient presents with thrombosis of the arteries of both legs. Such decisions should always be made at senior level and only after discussion with all those caring for the patient (including nurses in particular and often the primary care physicians). Close relatives must be in accord with the advice, but should never be made to feel that they shoulder the burden of the decision: that is the role of the surgeon.

In a 7-year experience of palliative care for patients with lower limb ischaemia in my own hospital, the median time from making the decision to death was just 3.5 days⁹. However, for those who seem likely to survive for a more prolonged period, it may be advantageous to involve a palliative care team in the management. Excellent analgesia, comfort measures and good pastoral care are all vital.

The threat of adverse publicity and medicolegal retribution now hangs over decisions to withhold active treatment. However, if the situation really has been discussed well with the patient and those close to them, these threats should be illusory. It is vital, however, that both the decisions and the discussions surrounding them are properly documented in the case record.

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Dealing with the rejected article

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Unfortunately the rejection of a submitted article happens to us all at some time or another. Indeed, it is fair to say that the vast majority of scientific publications are rejected initially by journal editors and it is the author's response to the comments of editors and referees which determines whether or not an article is ultimately published. Because very few 'first submissions' are published without further modification, the rejection of a manuscript should not be regarded as a personal criticism directed at the author by the referees and editors. Rejection paranoia should be unfounded.

Read the rejection letter carefully

How, then, to proceed when the manuscript has been returned with a polite letter of rejection from the managing editor? The first thing to do is to determine the nature of the rejection; that is, whether the article has been rejected totally or whether there is still an opportunity to resubmit after appropriate modification. Clearly it is extremely important to read the editor's rejection letter carefully. If the article has been rejected irrevocably by the journal then the editor's letter will say so and may well indicate the reasons. If this is the case, further communication with the editors in the hope of precipitating a dialogue through which you hope to persuade the editors to change their decision will invariably prove ineffective. The time is much better spent by careful examination of the reviewers' criticisms with the aim of responding to the comments and improving the manuscript before submission to an alternative journal. Even when the referees' comments appear to be supportive it should be appreciated that the editor's final decision results from a synthesis of two or more reviewers' critiques (which you will receive), together with each referee's structured assessment (which you will not receive) of such factors as originality, timeliness, study design, analysis of results, statistics and conclusions. There may even be factors such as pressure on space in the journal, which may weigh in the balance for a decision against acceptance. Editors will rarely reverse a decision for outright rejection no matter how powerful the arguments for reconsideration might appear to the authors.

A further good reason for careful reading of the rejection letter is that it might include an invitation to resubmit a modified version of the manuscript after responding to the

criticisms of the referees. Such an invitation does not imply that the resubmitted manuscript will be accepted automatically for publication. Such manuscripts are carefully scrutinized for appropriate modifications and most journals place a time limit (usually 2 or 3 months), after which any resubmission may be treated as a new submission. It may occasionally appear that requests from the managing editor (for example a request to shorten the manuscript) conflict with a suggestion by the referee (e.g. to expand the discussion to make additional points). Under such circumstances, if both instructions can be accommodated well and good, but remember that requests from the editors are likely to take precedence because they take into consideration the overall balance of the journal. If the editor suggests that the article is far too long for the message it has to transmit and recommends shortening each section by a certain percentage then you should do so. Failure to respond to the editor's requests will certainly jeopardize the chances of success of any resubmission.

Resubmission

If there is an invitation to resubmit a manuscript, the referees' criticisms will have to be addressed and the manuscript should be accompanied by a letter indicating where this has occurred. It is prudent to assume that the resubmission will be refereed again although this is not always the case if the criticisms are of a relatively minor nature. In general, each itemized comment should be answered, even if there are cogent reasons why the criticism may be irrelevant. Certainly you will need to provide very good reasons for not responding to a referee's comment if it is not intended to change the manuscript on this point. It then becomes a matter for the individual editor to determine whether or not a particular criticism can be ignored; this may well involve a further critical opinion before a final decision is reached about publication. The more additional referees that are brought into play, the more questions will be raised about the acceptability of the manuscript. Editors greatly value their expert referees and are more likely to accept their advice about publication of a manuscript than those implied by the authors. Above all, do not assume that addressing all the comments to your satisfaction will guarantee that the article is accepted. In particular, you should under no circumstances refer to the

article as being 'in press' until you have received the letter confirming acceptance for publication.

Do not be argumentative

The nature of the criticisms provided by the referees requires careful attention. Comments about style and presentation are readily dealt with, as are suggestions of further statistical analysis of the data reported in the original manuscript. It is much more difficult to respond to conceptual criticisms and those that relate to experimental design once a particular series of experiments or clinical studies have been completed and it is no longer possible to return to the original laboratory technology or experimental set-up. Fundamental criticisms of the study design that would mean repeating experiments or revisiting the clinical scenario are particularly difficult to handle. A value judgement will have to be made on whether it is worthwhile resubmitting the article (if invited to do so) or simply submitting it to a possibly less influential journal after incorporating a suitable comment into the manuscript that acknowledges the weakness of the study but explains the rationale for undertaking it in the manner described. This decision is a difficult one to reach and requires skill and experience. Junior authors are well advised to work closely with more experienced colleagues within a particular field to optimize the chances of a successful resubmission. Responding to criticisms about the conclusions reached from a given data set is again relatively straightforward, except where there are fundamental differences of opinion about the interpretation between the authors and the referees. It is then a matter of judgement on the part of the senior author to decide whether or not it is worth arguing the point with the editors, in the case of an invited resubmission to the original journal, or whether, on a point of principle, the article should be submitted to a different journal with the original interpretation intact. The latter is relatively unusual because, in general, a balanced view is feasible and enables a response to be generated which, with careful crafting, is equally acceptable to all parties. Again, however, an experienced senior view is invaluable.

Value the referee report

The reviewers' comments are of great value to the author even when a journal has rejected an article without inviting a resubmission. They provide a steer to improving the manuscript for submission to another journal. It is not unknown for the same referee to be asked to provide an opinion on a paper submitted to a second journal following rejection by the first. Accordingly, where possible and without prolonging the manuscript, it is useful to pre-empt

a repetition of the first reviewer's criticisms by incorporating them into the text of the new manuscript. When the rejected article has been returned, if it is to be resubmitted to an alternative journal then this should be done as soon as possible. Clinical science has a relatively short half-life and the sooner the article is in print the better. Whether or not the paper should be submitted to a journal that has a lower profile or impact factor than the one to which it was originally submitted is a matter of individual judgement. A decision to send it to a higher profile journal is risky because the chances of rejection will be correspondingly higher and this will inevitably incur delay in final publication. However, the choice of journal involves a consideration not only of impact factors but also of degree of specialization and other influences. It is important for authors to seek advice from others in the field as to the appropriateness or otherwise of a particular journal for a specific manuscript. A previous article in this series advises on where to send your manuscript. When modifying the manuscript for submission to a different journal it is absolutely critical to ensure that the new version is in the correct 'house style' for the journal to which it is to be sent. Editors take an understandable dislike to manuscripts submitted in a format that is very obviously that of a competitor journal, even though they appreciate that such resubmissions occur commonly. Failure to adopt the correct journal style gives an impression of imprecision and sloppiness on the part of the author which is unacceptable.

Conclusions

The editor's letter of rejection and the copies of the referees' critiques contain important pointers to the rewriting of the rejected manuscript in a form that may make it acceptable for resubmission either to the original journal or to an alternative one if the rejection is irrevocable. Considerable skill and experience will be required to construct a suitable response to criticisms of design and suggestions of flawed experimentation, which for practical reasons cannot be revisited. Under these circumstances the advice of senior colleagues who have a feel for the journal's expectations and reactions to what may be challenging conflicts of opinion are invaluable. Finally, authors should be reassured that the majority of articles are published somewhere eventually. Do not let your rejected manuscript gather dust; the longer you temporize the lower are the chances of publication. Remember that each submission-rejection cycle may take from 3 to 6 months. Be resolved and persistent and you will get there eventually. Selection of the appropriate journal for the first submission is almost as important in avoiding rejection as having the idea and undertaking the research in the first place!

Research misconduct: diagnosis, treatment and prevention

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Introduction

Research misconduct has probably existed for as long as researchers have researched. The temptation to enhance or embellish a research finding with a few extra experiments that were never done or to trim away 'inconvenient results' has been there as long as people have had a desire to answer scientific questions through experimentation. Even outright fraud is not a new phenomenon; there are examples going back as far as Mendel's work several centuries ago.

During the past decade, however, research misconduct has been placed firmly in the public eye with increasing coverage of cases by daily newspapers concerning the sacking of academics by universities and a substantial number of disciplinary hearings by the General Medical Council (GMC)¹.

A further indication of the seriousness of the problem is reflected by the development in many countries of agencies to deal with cases of suspected research misconduct, such as the Office of Research Integrity in the USA and similar bodies in Scandinavia, other European countries and Australia. There is the impression that research misconduct in all of its forms is on the increase and, because of the serendipitous nature of many of the discoveries of misconduct, many now feel that we may be looking at the tip of a rather large iceberg.

What is research misconduct?

There are a multitude of misdemeanours that are commonly brought together under the headings of research and publication misconduct². At the milder end of the spectrum there are sins of omission; an example would be when experimental design is inadequate to answer the questions raised in the study. Similarly, the inappropriate use of statistical analyses may produce inaccuracies both in the final results and in the conclusions reached. This occurs through ignorance but also by intent. Selective presentation of results through data suppression or exclusion may similarly influence the research findings to produce apparently 'clear-cut' results but which are at the same time misleading. It is always easier to write a paper when everything fits neatly together! Finally, the major offences

of fabrication, falsification and plagiarism constitute outright research fraud. It is these major crimes that have been picked up avidly by the daily press and in the UK have resulted in doctors being struck off by the GMC. Some scientists argue that even overtly fraudulent research is not as dangerous as many would like to have us believe, since others will repeat the work and, if false, will eventually put the record right and make this clear in the biomedical literature. I would argue that this 'soft line' makes a complete nonsense of the fundamental premise on which scientific research is based, namely 'honesty'. In addition, it is a deplorable waste of time and resources to prove that fraudulent research is false. In addition, damage can be done before the truth about falsified research eventually comes to light, as illustrated by a paper published in 1993 in the *British Medical Journal* which was subsequently retracted last year after 5 years of exposure in the public domain. This paper was of sufficient public health importance to change the delivery of services in a region of the UK.

There are instances when there are no questions about the way in which a piece of research was conducted, but in the process of preparing the manuscript for publication, and the manner in which the paper is presented to a journal, the authors commit publication misconduct. A common problem centres around authorship. It is now well recognized that individuals' names often appear on a paper whose contribution to the work is questionable, so-called 'gift authorship'. The Vancouver group of editors has published guidelines on what constitutes authorship which, for example, would exclude a widely held custom to include the head of department as a 'courtesy' (Table 1)³. There is now a move away from authorship towards contributorship, in which each individual outlines at the end of the paper his or her individual contribution to the work. There would also be a guarantor who would take overall responsibility for the veracity of the paper⁴. Disputes between authors are also common, ranging from failure to obtain approval from all authors before the final manuscript is submitted to a journal to changes in authorship or the order of authors during manuscript revisions.

Some authors still submit papers simultaneously to two journals (dual submission), while others attempt to identify

Table 1 Authorship

Authorship credit should be based only on substantial contributions to:
(a) Conception and design or analysis and interpretation of data; and to
(b) Drafting the article or revising it critically for important intellectual content; and on
(c) Final approval of the version to be published
Conditions (a), (b) and (c) must all be met
Participation solely in the acquisition of funding or the collection of data does not justify authorship
General supervision of the research group is also not sufficient for authorship

From Reference 3

'the minimal publishable unit', sometimes referred to as 'salami slicing'. Most editors would prefer to see a substantial manuscript containing a cohesive story rather than a string of minor contributions in a variety of different journals.

Failure to declare conflicts of interest is another aspect of publication misconduct. Conflicts include direct or indirect financial support for the study, consultancy agreement with a study sponsor, a holding of any patents relating to the study and any other mechanisms by which financial benefits might accrue as a result of publication of the study. It has been said that 'disclosure is almost a panacea'.

Does research misconduct exist in Britain?

In 1988 Stephen Lock, then Editor of the *British Medical Journal*, published a paper summarizing the findings of a survey that he conducted in 29 medical institutions in Britain from which there were 79 respondents, many of whom were professors of medicine and surgery⁵. More than half knew cases of research misconduct, many of which involved senior academics, and only a minority of the cases had been investigated. He concluded that there was a definite problem in Britain and that the results of this survey were likely to be an underestimate.

During the past 5 years a number of major fraud cases have been drawn to the public's attention and during the past 2 years the GMC has received 31 complaints relating to alleged drug trial misconduct or fraud. However, it must be emphasized that the size of the problem in the UK remains completely unknown as current impressions rely entirely on the misdemeanours detected.

Who are the fraudsters?

Research misconduct has been committed across the age-experience spectrum. Fabrication of clinical trial data,

usually the addition of fictitious patients to a randomized controlled trial, may involve a relatively naive, inexperienced investigator, such as the general practitioner or a senior hospital consultant¹. In some instances the motivation is financial, driven by the knowledge that the more patients recruited to the study, the greater the rewards. Studies driven by the pharmaceutical industry are usually monitored closely such that detection of research fraud becomes evident when clinical report forms cannot be matched to patients' clinical records. Sometimes fraudulent clinical investigators will persuade research associates to collude with the fraudulent process.

Another category of fraudster is the young laboratory scientist who succumbs to the pressure for academic success and promotion, and the institutional demands to secure research funding. These individuals are often medically qualified, male, and working in a distinguished institution within a productive research group. The individual almost invariably has a list of publications that is growing at a rate well beyond that normally expected from someone at that stage in his or her career. Research data may be fabricated completely or falsified by selected deletion and/or supplementation. Other laboratory colleagues often suspect that such a person is working in a dishonest way but are generally disinclined to come forward as the 'whistle blower'.

Thus, research and publication dishonesty crosses all age groups, disciplines and levels of seniority.

Diagnosis

Serious research fraud is usually discovered during the formal audit or monitoring process of randomized controlled trials, when all patients apparently recruited into the study cannot be accounted for from a search of independent medical records. Fraudulent clinical trials have also been detected after publication, often when there are some unusual features to the study. Surprising, unexpected results emerging from an apparently large single-centre study written up by a single author might attract attention. Published work may come into question when an investigator is found to have committed research misconduct and then previously published fraudulent work is revealed following a systematic review of the contents of the author's curriculum vitae. The other important route by which research fraud is detected is through a 'whistle blower', commonly a colleague in the same or a closely related department. Although there are many examples of when 'whistle blowers' have subsequently suffered more than the accused, there is now a firm legal framework to protect people in the workplace who become concerned about the behaviour of colleagues. We all have a responsibility to be

vigilant about the quality of research with which we are directly or indirectly associated.

If you have suspicions that a colleague may be producing research findings dishonestly, the most important first step is to ensure that you obtain evidence of your suspicions before reporting this to a senior colleague. In some instances it may be entirely appropriate to discuss this with the person concerned, particularly if you feel that the main problem is 'trimming and pruning', which the individual may be pursuing out of ignorance. Similarly, if there are potential misdemeanours regarding publication ethics, such as dual submission or redundant publication, then these should be dealt with by open discussion. However, if the misdemeanours are of a more serious nature, such as fabrication or falsification of research data, then you must be able to provide evidence of the misdemeanours before reporting to a higher authority. I have been approached by potential 'whistle blowers' who have waited weeks or even several months to ensure that their suspicions are well founded. At this point you should discuss this with your head of department, although if that individual is directly involved with the research it may be more appropriate to discuss your concerns immediately with the head of the institution. At this point a preliminary enquiry should be performed along the lines described in the Royal College of Physicians Working Party report⁶ or as described in a document produced by the Medical Research Council (MRC), which describes a procedure for enquiring into allegations of scientific misconduct within MRC units⁷.

Research and publication misconduct is also detected by journal editors and reviewers. In my experience as an editor of a specialist journal, sharp-eyed reviewers have drawn my attention to the majority of cases of misconduct that I have come across in the past 3 years. However, in almost every case there has been an element of serendipity about the discovery. For example, in one case of plagiarism I just happened, by chance, to send the manuscript to a reviewer whose papers had been plagiarized. How many other manuscripts have passed through the system and escaped detection because the reviewer did not have such an intimate knowledge of the text of related papers? Redundant publication and 'salami slicing' is again usually detected by expert reviewers who know their subject well. On several occasions we have by chance sent a manuscript to a reviewer who had been sent a closely related and, in some cases, an identical manuscript by the same authors from another journal, simultaneously. In this case publication can be stopped but if the manuscript had been sent to another reviewer, who had not seen the closely related manuscript, then both manuscripts could have entered the public domain with inevitable redundancy. Thus, the detection of publication and research misconduct seems to carry with

it a large element of chance, and many editors of biomedical journals suspect that only a small proportion of misdemeanours are detected. It would appear that crime does pay! Diagnostic approaches would thus seem to be inadequate and, given the obvious limitations that a 'whistle blower', editor or reviewer might have, perhaps we should focus our attention more on treatment and prevention.

Treatment

When serious fraud, such as fabrication of controlled clinical trial data, is detected, the person or persons concerned are reported to the GMC. If a preliminary review of the evidence suggests that there are sufficient grounds to proceed, the GMC holds a full enquiry and, if the defendant is found guilty, this might result in exclusion from the Medical Register. For lesser crimes and those involving non-clinical scientists, a 'whistle blower' or journal editor might refer the case to the head of the investigator's department or institution. Reporting an individual to the head of an institution, however, may not necessarily produce a satisfactory outcome as there may be a conflict of interest. For example, the senior author might be a prominent clinical academic within the institution and possibly even a personal friend of the Dean. There are a number of instances of alleged serious research misconduct that have been 'silenced' within the investigator's institution. It is difficult to feel confident that internal enquiries into alleged research misconduct held 'in camera' will reliably get at the truth when for the institution there is so much to lose and little to gain.

Editors face some difficult issues when they suspect or detect research fraud. Once a journal has published a paper that is subsequently shown to be fraudulent or redundant then the paper is retracted and a notice to that effect published in the journal. This places the case in the public domain and the authors are exposed. In serious cases the editor may, in the case of clinical investigators, refer the matter to the GMC. A recent study has shown, however, that this does not stop the paper being cited in the literature for many years, usually without making any reference to the fabrication or falsification contained therein⁸.

It is, however, more difficult to know precisely how to act when research misconduct is suspected during the peer review process before publication. The most common editorial response is simply to reject the manuscript. This is clearly unsatisfactory and one might argue that the editor has not fulfilled his/her duty as a custodian of the biomedical literature because it is likely that the paper will merely be submitted to another journal. Some editors have taken a 'hard line' and have placed sanctions on all authors who engage in redundant publication, such as by refusing to

Table 2 Prevention of research and publication misconduct

Education	Research training Research ethics Publication ethics
The research	
Protocol driven	Define roles
Establish contributors and collaborators	Agree protocol
	Agree presentation of results
Define methodology for data analysis	Statistical advice
Ethical approval	
Project and personal licence (Home Office)	Guarantor
Supervision	Communication
	Ensure good clinical practice
	Record keeping
The publication	
Disclose conflict of interest	
Disclose previous publication	
Approval by all contributors	
Submit to one journal at a time	
Assume research data audit	

accept further submissions to the journal for a set period, say 3 years⁹. Editors who are members of the Committee on Publication Ethics (COPE)¹⁰ have produced some guidelines on good publication practice (available in the 1999 COPE Report¹¹ or on the COPE website <http://www.publicationethics.org.uk>), which set down a hierarchy of sanctions that editors may publish in their journals and use judiciously such that 'the punishment fits the crime'. These might range from a firm letter to the author pointing out the breach of publication ethics when it is felt that an error occurred through ignorance and not malintent, through to tougher sanctions such as limited access to the journal for a given period as described above or ultimately to referral of the matter to the author's head of institution or directly to the GMC. The Royal College of Physicians in London and the MRC have produced guidance on the investigation and prevention of research misconduct^{6,7}.

Prevention

Although it might be hoped that investigators would be less inclined to commit research and publication misconduct if they knew the chances of getting caught and punished were increased, ultimately the route to prevention must be through education and reaffirmation of the still widely held belief in the principle of research honesty. All students entering a period of research should receive not only instruction on research design, methodology and laboratory techniques but also guidance on the fundamentals of

research and publication ethics (Table 2). Research should be protocol driven, and contributors and collaborators should define their roles before the work is commenced. Any protocol changes should be discussed and agreed by all of the participants. Statistical advice should be sought, where appropriate, during the planning process and it goes without saying that all studies involving human subjects should be submitted to an appropriate research ethics committee. There is a sense that at least some of the instances of research misconduct could have been avoided by closer supervision of the project. Supervisors may find themselves increasingly distanced from the laboratory bench or the patients in the clinic, which can make it difficult to check the veracity of the primary data. Review of research results should involve examination of the primary research record, which may be the laboratory record book or patients' medical notes. Impeccable record keeping is an essential component of good research.

The ethics of publication are as important as research ethics. All authors should see the final manuscript before submission and each should sign the declaration confirming the originality of the work. An article should be submitted to only one journal at a time. Authors should disclose any potential conflicts of interest, particularly if the opinions expressed in the manuscript could be influenced by financial incentives through sponsors. Authors should also disclose the nature of any related publications that have been published recently or that are under consideration by another journal. There are times when it is entirely reasonable to publish some previously published data but this should be done with the full knowledge of the editor and reviewers, so that a full assessment can be made of the extent of any potential overlap. In the future, original research may be submitted to random audit before publication and it is therefore wise that authors assume that they may be asked to produce their primary data to support the work described in a manuscript.

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Epilogue: key considerations in surgical publishing

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We hope that a few of you will have read this series on surgical publishing. In this epilogue we would like to leave you with a few key considerations.

Considerations on why to publish¹

Egoistic motives include the strive for academic and/or professional promotion, which, in turn, may be associated with financial gain, the will to improve one's knowledge and judgement, and the development of professional contacts. Altruistic motives are the desire to generate and disseminate knowledge.

The more you write and publish the longer is your list of publications. The more publications you have the better should be your writing ability. The better you write the greater the chance of your papers being accepted by leading journals. The more you are published in top journals the greater likelihood of your papers being cited by others. The more you are published and cited the higher your score on the impact factor and citation index lists.

While most authors will not admit that one of the strongest motives to writing is seeing their own name in print, this is the truth and nothing is wrong with it. The sum of all above is 'fame and fun' as Richard Feynman, the Nobel laureate physicist, called it 'The pleasure of finding things out'.

Considerations on what to write²

Don't fool yourself. Your first paper won't appear with earth-shattering findings in the *New England Journal of Medicine* or *The Lancet*. The first published paper of most giants in surgery was a case report or a limited retrospective clinical experience. Start modestly and aim higher later.

Any of your patients can be written about, especially if offering any novel aspect and if it is thoroughly researched and well written. Do not shy away from reviewing and writing about your or your department's clinical experience if you think that it can offer another perspective. Even if published 'only' in one of your regional or national journals it may be of great value to your community. Not only

'perfect results' or 'positive findings' of a study need to be published. Admire the zero mortality and morbidity rates from the ivory towers – published in the *Annals of Surgery* – but try to write up your centre's more modest experience and results. In order for you and us to improve, we need to know how are we doing in the 'real world' away from the ivory towers.

Before deciding 'what should I write' you should know 'what has been written'. Doing so, very soon you will realize that you could do it as well, or even better. Follow Faulkner's advice: 'Read, read, read everything – trash, classics, good and bad, and see how they do it. Read! You'll absorb it. Then write'. Whenever you are bothered by a dilemma for which you cannot find the 'correct' answer, think that this is something to be researched, better defined and, perhaps, written up. Don't be lazy, go to the library and search and cross-search in textbooks and journals. Always use the electronic Pubmed–Medline search machines. The condition or dilemma you are confronted with is probably more common than you thought.

Considerations on where to publish³

Your chief goals are the greatest readership, a prestigious, high-impact journal, speedy editorial process and a fair chance of acceptance. The potential 'market' for your manuscript is huge. It is not the end of the world if the *BJS* rejects your masterpiece. If you try hard enough each of your manuscripts will eventually be accepted by some journal.

Choose the audience (general, specialized, local?), always consult the 'instructions to authors' of the journal(s) targeted and assess objectively the value of your paper. You do not want to submit a technical paper to a theoretical journal or a banal case report to *The Lancet*. Focus on a limited list of journals, which represents a spectrum of qualities tailored to the value of your manuscripts. With time, you will learn to satisfy their editors while the latter may eventually learn to appreciate your work.

The key elements of a successful submission are to assess the value of your manuscript, to understand the publishing

market, to study the target journal(s), to tailor your manuscript to the latter and, most importantly, to get learned advice from someone who is very experienced.

Considerations on the generation of an idea⁴

While ideas are plentiful, only the novice and naive think that all ideas are publishable. Only by repeatedly formulating ideas worthy of publication and bringing them to fruition will you be able to shade off your publishing naivety. It was Ernest Hemingway who said: 'The most essential gift for a good writer is a built-in, shockproof, shit detector. This is the writers' radar and all great writers have had it'.

A review article has to 'close a gap' that has not been well covered in recent major texts and journals. Ask yourself: is the topic of enough interest to capture the reader and the reviewers? Is it controversial enough to allow a stimulating discussion? Review articles, as original studies, can be tailored to the various journals. Leading journals may accept a review by the world's expert on the laparoscopic management of pancreatic carcinoma. There are, however, low-key journals that may publish your educational review on postoperative fever. Beware of claiming the 'first reported case of...'. What you think has been never published may be rare, what you suggest is rare may actually be quite common, provided that you search the literature thoroughly.

The operative technique you wish to describe has to be novel, offering a new solution to an old or new problem. Resist the temptation to perform a surgical gimmick only for the sake of its publication (e.g. laparoscopic resection of sebaceous cyst). As Sholem Asch said: 'Writing comes more easy if you have something to say'.

Not only surgical giants and 'known authorities' in their field have the right to express their opinions. If you have something valuable to say, say it clearly. It might not be accepted as an editorial or a leading article, but as a 'letter to the editor' it has a fair chance. In fact, a well edited correspondence section is one of the most well read parts of any journal.

Considerations on getting started⁵

Before you start, have a general idea of what you want to say. Preparing an outline may help. Simmer the outline for a while but do not overcook it for there may be others out there with a similar idea and plan. At this stage the results of the study must be ready. Check and recheck all numbers and figures, avoiding any embarrassing discrepancies and errors.

Tame the relevant literature by whatever means. Highlight or underline the points you wish to use, and then organize them in tables or piles. A large desk or floor is useful. Get the full text version of the papers you plan to use in your bibliography. Citing only Medline abstracts is easier but it means that you cheat yourself and the readers. According to Arthur Baue: 'Citation of secondary sources results in continued myths, misquotations, and incorrect citations. It is frustrating to seek a reference that is incorrectly cited. It is fun however, to track down and read the primary source'.

Instead of sitting in front of a blank sheet or screen take a walk, think and talk to yourself. Then try again. Writing is tough for all of us. Even Molière said: 'I always do the first line well, but I have trouble doing the others'.

Considerations on writing the manuscript⁶

The materials and methods (what you did) and results (what you found) are the body of your manuscript; start with them. Only then add the skeleton – introduction (why you wrote this paper) – and the heart – discussion (what you feel about it). The abstract comes last, as stated by Pascal Pennées: 'The last thing one settles in writing... is what one should put in first'. The abstract alone should convey to the reader all that you did and found, and what it means. If published, most readers will never see the full version of your paper but only the electronic version of your abstract. 'There is no better writing exercise than composing an abstract' (Arthur Baue). Avoid any discrepancies between the abstract and the body of the paper because it irritates the reviewers and biases the validity of the report.

Your manuscript should be 'self-contained'. A statement such as 'the methods were described previously' might enrage the reviewers and frustrate the readers. Avoid duplications and redundancies; say what you have to say once only. Do not disclose results in the introduction, do not shift portions of the materials and methods into the results, do not repeat results in the discussion, do not introduce results or other studies in the discussion, and do not repeat data shown in the text in the tables.

Do not be biased in selecting literature for your bibliography. Be aware that the reviewers of your manuscript are experts in their field; they know the relevant literature and may 'search' it on their computers, immediately revealing your omissions. Never, we repeat, never cite a reference without reading it entirely for it is misleading and an intellectual crime. US authors tend to cite US papers and British authors tend to cite British papers. You do not want to be narrow minded in the global era: cite any study that is appropriate.

Be original. Do not plagiarize; always use your own language. It is easier to 'copy and paste' entire paragraphs from the Medline but you do not want to do this. Your discussion has to focus on your own results and compare your findings with those of others. It should not be an exhaustive review of the literature if it is not a review article. Be frank; by disclosing in the discussion the deficiencies of your study you can disarm malicious reviewers.

Whenever you sit down – or stand up (*à la* Hemingway) – to continue with the manuscript, reread it from the beginning. Anthony Trollope stated: 'By reading what he has last written, just before he recommences his task, the writer can catch the tone and spirit of what he is then saying...'

Surgical publishing may deal with boring material but must not be in itself boring. Take Voltaire's advice and be brief: 'The secret of being a bore is to tell everything'. Use simple language and try to be true rather than bombastic.

Considerations on the foreign author⁷

The assumption or 'excuse' that your paper was rejected because English is not your mother language, or because you are a foreigner, is a self-serving nonsense. Reviewers are keen and able to recognize a valuable contribution even if written in broken English. Editors will do all they can to improve your article, if they consider it publishable. If you are able to complete a reasonable manuscript in your own language, why should it not be possible to do so in English? If you are versed with the basics of scientific writing in your own language, doing so in English will be much easier as it is the novelty of your idea, the quality of your study and the organization of your manuscript that really matters, more than your mother language.

Publish also in the 'local' journals of your country. Even if Matthew said that 'a prophet is not without honour, save in his own country', being famous internationally and poorly known locally negates the purpose of your writing. Beware of professional non-medical translators who 'translate' the meaning of your thoughts into beautifully sounding English gibberish. The 'importance' of publishing varies of course between different countries. 'In America only a successful writer is important, in France all writers are important. In England no writer is important. In Australia you have to explain what a writer is' (Geoffrey Cotterell).

Considerations on the final product⁸

A surgical paper, like yummy pasta, should be well prepared but *al dente*. When overboiled it is boring to the taste buds as well as to the reader. Read and reread your final manuscript. Put it aside for a few days, read it again, then reread it aloud.

As Fran Lebowitz wrote: 'In conversation you can use timing, a look, inflection, pauses. But on the page all you have is commas, dashes, the amount of syllables in a word. When I write I read everything out loud to get the right rhythm'.

Choose the title carefully; let it reflect the essence of your paper while being catchy but not too gimmicky. Walker Percy said that 'a good title should be like a good metaphor; it should intrigue without being too baffling or too obvious'. Arthur Baue suggested that 'the title is the message, not the medium'. However, according to Hemingway: 'Getting a title is a lot like drawing cards in a poker game'. 'If the title is a rhetorical question, the answer is always no. If the answer was yes, the authors would have stated it accordingly' (Arthur Baue).

How lovely it feels to seal the envelope over your finished manuscript. Be optimistic but not too hopeful. According to J. B. Priestley: 'Most writers enjoy two periods of happiness – when a glorious idea comes to mind and secondly, when a last page has been written and you haven't had time to know how much better it ought to be'.

Considerations on what an editor wants or expects from authors⁹

The reviewers and editors would like your manuscript to be perfect but this is seldom the case. The farther your manuscript is from the ideal, the more irritating it is to the reviewers, and the more likely it is to land in the garbage bin. Having had your manuscript battered by the reviewers, your last hope is that the editors will detect its virtue. Editors, however, have to read numerous manuscripts. 'That is why the message of a manuscript must be clear and up front. A subtle message will be lost, as it probably should be' (Arthur Baue).

Reviewers are busy people; your manuscript must not exasperate them. Be sure to follow the instructions to authors particular to the journal to which the manuscript is sent. See that your manuscript is clearly printed and copied. Start each section on a new page, and use paragraphs and subheadings. Sloppy presentation correlates often with sloppy contents. The editorial process is lengthy. Be patient. Wait at least 3 months before calling the editorial office; only masochists call for bad news.

Considerations on politics in surgical publishing¹⁰

Decide about the list of authors before conducting and writing up the study. Doing it at the end causes trouble. The number of authors should correlate with the magnitude of the manuscript; for a review article or a case report to have

more than three authors is ridiculous. The three most 'prestigious spots' on any list of authors are the first, second and last. Divide them between the three people who contributed to the paper most. The 'lonely author syndrome' of a large clinical study means that the author failed to acknowledge colleagues who deserve coauthorship.

Do not provide your colleagues with 'gift authorship' which, as free lunches, are rarely appreciated. They would add it to their curricula vitae without even bothering to read it. Do not accept authorship from others without having contributed significantly to the paper. Remember that your reputation is more important than your list of publications. 'You can fire your secretary, divorce your spouse, abandon your children. But they remain your coauthors forever' (Ellen Goodman).

Considerations of the editorial desk¹¹

Contrary to what you may believe, manuscripts submitted by members of the editorial board of a journal are scrutinized as severely as yours. Their only advantage is that they know better how reviewers and editors think and what they want. You will know it as well by reading this entire series again.

We agree. Editors and reviewers are a pain in the ... but, nevertheless, without them our world of scholarship would be chaotic and meaningless. But go on, bash at your critics, most writers do. 'Nature fits all her children with something to do; he who would write and can't write, can surely review' (James Russell Powell).

Considerations on the rejected article¹²

Do you wish to know what the reviewers who rejected your paper are like? Look at your local academic leaders and professors: bright, talented, honest but occasionally prejudiced, biased and even dogmatic. Do not waste energy on anger and self-pity but promptly revise and resubmit your manuscript based on the reviewers' comments with which you do agree. 'Listen carefully to first criticisms of your work. Note just what it is about your work that the critics don't like – then cultivate it, that's the part...that's individual and worth keeping' (Jean Cocteau).

Do not despair. Somewhere along the line, perhaps even at the third or fifth journal, there will be someone who understands your idea and message. For 'in literature, as in love, we are astonished at what is chosen by others' (Andre Maurois). When rejected, do not argue with the publishers. That you are right and they are wrong won't help. Do not imitate Henry James who, when asked to delete a few words

from a 5000-word article, said: 'I have performed the necessary butchery. Here is the bleeding corpse'.

Do not park the rejected manuscript at your driveway to accumulate rust. Trade it in as soon as possible and as many times as required.

Considerations on ethics of writing¹³

Even the best salami loses flavour at its cut edges. The more it is sliced into tiny pieces, the more of its original taste you lose. Likewise, do not slice your study into tasteless thin pieces. Fish tastes best when fresh out of the water. A day later, at brunch, its bitterness has to be disguised with mayonnaise. It is the same with your study; if reprocessed – duplicated in another journal – it will offend your colleagues and may even cause food poisoning.

Words, when shaped into sentences, paragraphs and ideas, become the intellectual property of their original author. The best antidote to plagiarism is always to cite your sources. 'If you copy from one author it's plagiarism. If you copy from two, it's research' (Wilson Mizner).

Conclusions

We hope that you will become a successful surgical writer and, sooner or later, you will do it naturally, in your own way. As Somerset Maugham said: 'There are three rules for writing...unfortunately, no one knows what they are'. And to the critics of this paper, who surely will claim that we have used too many quotations, let us cite from Winston Churchill: 'It is a good thing for an uneducated man to read books of quotations'.

Obviously, there is nothing new in the ideas included in this series, for scientific writing is ageless. Our aim, however, was to digest the essence of publishing specifically for you, the surgeon. To paraphrase Baue¹⁴: we wish to offer to the young or old surgeon to put words on paper, write and rewrite, and rewrite again. Surgical literature needs all worthwhile contributions, reports and ideas.

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British Journal of Surgery Research Bursaries 2000

The Council of the *British Journal of Surgery* is delighted to announce the award of Research Bursaries to the value of £10 000 to the following:

Mr I. S. Currie, University of Edinburgh.

Intestinal barrier dysfunction and major sepsis in orthotopic liver transplantation.

Mr P. C. Haggart, Birmingham Heartlands Hospital.

The detection of circulating bacterial DNA and multiple organ failure in patients undergoing repair of ruptured abdominal aortic aneurysm.

A total of 79 applications was received this year for the bursary awards. As usual, the standard was extremely high and the marking process has been very difficult. The following submitted applications that were highly commended by the judges:

Ms J. Bingham, University Hospital, Belfast

Mr P. Burns, Heartlands Hospital, Birmingham

Dr F. U. N. Din, University of Edinburgh, Edinburgh

Miss D. M. Hansrani, Freeman Hospital, Newcastle-Upon-Tyne

Miss C. Murphy, St James's University Hospital, Leeds

Mr D. A. O'Reilly, Derriford Hospital, Plymouth

Mr A. Smith, University Hospital, Nottingham.

The Council would like to thank all those who submitted entries for the Research Bursaries. A decision about next year's awards will be made later in the year. Watch out for news about the plans via the *British Journal of Surgery* website (www.bjs.co.uk).

J. J. Earnshaw
Associate Editor

Liver fracture and bleeding

At laparotomy for blunt abdominal trauma a surgeon in a district general hospital encounters a fractured bleeding liver. How should the problem be handled? Professor J. E. J. Krige of Cape Town, South Africa, replies.

The surgeon who unexpectedly encounters a major liver injury during a laparotomy for trauma will need to make several rapid critical decisions. The objectives are self evident and clear: stop the bleeding by the simplest means possible, remove devitalized liver tissue, and suture damaged blood vessels and bile ducts. But how should these strategies best be implemented? This dilemma is approached largely from the viewpoint of most general surgeons who work outside regional trauma centres or specialist hepatobiliary units and who seldom deal with major liver injuries and may have limited resources.

The surgeon has a variety of options to control liver bleeding. These range from fairly simple to increasingly demanding techniques, depending on the magnitude of the liver injury. The choices include diathermy or argon beam coagulation, the use of topical agents such as fibrin glue or Surgicel (Ethicon, Livingstone, UK) (for superficial injuries), inflow occlusion of the portal triad (Pringle manoeuvre), liver packing, hepatorrhaphy, hepatotomy and direct vascular suture, resectional debridement, partial or anatomic resection, and total hepatic vascular isolation with venovenous bypass. Other procedures, including hepatic artery ligation, atriocaval shunting ("more authors than survivors") and sternotomy for exposure, are now thankfully obsolete. The level of intervention will ultimately be influenced by the surgeon's experience, local resources and the facilities available. The key is to use the most effective yet simplest option for a specific situation.

Initial management is critical. The greatest immediate threat is exsanguination¹. The absolute priority is rapid control of bleeding. The fracture is closed by manual compression and tamponade maintained by packs and pressure². This may be supplemented by inflow occlusion (Pringle manoeuvre) using an atraumatic vascular clamp across the portal triad. Effective intraoperative resuscitation is crucial. Pack pressure is maintained until the anaesthetist has fully restored intravascular volume. Premature attempts to evaluate the extent of the injury and mobilize the liver before adequate resuscitation may lead to catastrophic blood loss with ensuing hypotension, coagulopathy, acidosis, hypothermia and unnecessary death. These potential effects should be anticipated and countered by providing warm intravenous solutions, the freshest possible blood,

fresh frozen plasma, platelets, cryoprecipitate, a raised ambient theatre temperature and correction of metabolic abnormalities.

If bleeding has stopped after careful pack removal and release of inflow control, the surgeon should do no more. If bleeding persists, adequate exposure and a clear view of the injury become essential. Intermittent inflow release and effective suction allow identification of deeper bleeding sites which are controlled by direct suture, ligation, parenchymal suture or a mattress liver suture³. If bleeding still continues, experience and judgement are essential in the decision whether to advance to the next level of intervention. Extending a liver fracture to improve exposure can incur daunting haemorrhage and morbidity, which may exceed any anticipated benefit. If bleeding is not controlled by portal triad occlusion, major vena cava injury or atypical vascular anatomy is likely. Posterior right lobe injuries are relatively inaccessible and require extension of the abdominal incision, fixed subcostal retraction, and full mobilization of the right lobe to provide access to the inferior vena cava and right hepatic vein which can be digitally controlled. Complex venous injuries may require total hepatic vascular isolation⁴.

Non-anatomic resection is used to remove a partially attached and often ischaemic portion of liver peripheral to a fracture line, which in effect is completion of a *de facto* traumatic resection. Resectional debridement implies removal of non-viable liver bordering an injury. Anatomic resection performed through conventional anatomic planes unrelated to the lines of fracture is seldom necessary. It is justified only in severe liver injuries in which the lobe is shattered and conservative measures are bound to fail because of devascularization or proximal biliary injury. Formal resection in an unstable coagulopathic patient becomes a formidable undertaking and is not recommended for the occasional liver operator.

For the surgeon encountering a major liver injury in a district hospital, perihepatic packing should be the first option when lesser procedures do not control bleeding. If packing controls the bleeding, no further intervention is necessary. The packs are left in place, the abdomen is closed and definitive treatment deferred until a surgeon who can perform the required surgery is available or the patient can be transferred to a major trauma or hepatobiliary centre. Even for the experienced surgeon, if bleeding is controlled, discretion and packing may be the better part of valour. Other factors also influence the decision to pack. If the patient is acidotic (pH below 7.2), hypothermic (body

temperature below 32 °C), coagulopathic or has had a massive transfusion (more than 10 units of blood), the liver should be packed, the abdomen closed and the patient returned to the intensive care unit. Blood volume is restored, the patient warmed, and the acidosis and coagulation defects corrected.

The technique of perihepatic packing is important. Sufficient packs should be used to provide effective uniform pressure. In this hospital a 'six pack' is generally used. An attempt should be made to restore the liver contour to normality by closing the defect and providing tamponade by external pressure with packs above and below the liver². Too many packs may cause increased intra-abdominal pressure, caval compression and acute renal failure. Intra-abdominal pressure should not exceed the critical limit of 25 mmHg. An important practical point is to avoid intrahepatic packing because packs forced into deep liver fractures aggravate the injury by increasing the size of the rent and holding it open, as well as tearing small hepatic veins.

Early recognition of severe injuries, the judicious use of packing to control bleeding in complex hepatic trauma, and referral to a specialist team experienced in liver trauma management are now essential components in the handling of major injuries¹. Further intervention may be formidable, requiring sophisticated equipment, and expert anaesthesia, surgery and intensive care. Postoperative complications are

common; the modern management of severe liver injuries has evolved into a multidisciplinary approach with increasing reliance on ultrasonographic, angiographic⁵ and interventional endoscopic techniques to drain septic collections, embolize intrahepatic bleeding and stent bile leaks.

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Neosphincters in the management of faecal incontinence

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Background: Surgical treatment of end-stage faecal incontinence has its origin in the early 1950s. Interest has been revived as a result of technical advances achieved in the recent past. The purpose of this article is to review the principles that underlie the use of skeletal muscle transposition around the anal canal and of electrical stimulation in the treatment of incontinence, and to explore new methods of treatment of this condition.

Methods: A literature search was performed using Pubmed and Medline, employing keywords related to treatment of faecal incontinence by neosphincter reconstruction. Basic science and clinical aspects of neosphincter reconstruction were gathered from relevant texts, original articles and recently published abstracts.

Results: The electrically stimulated gracilis neoanal sphincter seems to be the popular choice of biological neosphincter. It is more likely to produce higher resting anal canal pressures than the unstimulated neosphincter, and hence improved continence. However, electrostimulator failure may result in explantation in a proportion of patients. Impairment of evacuation is a functional setback in approximately one-third of patients with the gracilis neosphincter. Overall, improvement of continence may be expected in up to 90 per cent of patients according to some reports. By contrast, experience with the artificial neosphincter, which is less expensive, has been limited to a few tertiary centres across the world. Reported continence of stool is 100 per cent, and that of gas and stool 50 per cent, following implantation of the artificial sphincter. Both of the above operations have been associated with implant-related infection and impaired evacuation.

Conclusion: Neoanal sphincter operations are technically demanding, require a considerable learning experience and should be confined to specialist colorectal centres. Patients are likely to benefit from a plan that incorporates preoperative counselling and a selective approach.

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Introduction

Continence of gas and stool is the ability to retain and expel gas and faeces at a socially appropriate place and time. Continence depends on a number of factors, notably normal anatomy and function of the internal and external anal sphincters and of the pelvic floor muscles, and normal anal and rectal sensation. Other variables that play a part in preserving continence are stool volume and consistency, intestinal transit and normal mental function. The community prevalence of faecal incontinence in Europe and the United States is approximately 2 per cent^{1,2}. Comparable data are not available for developing countries. Previously published data suggest a global incontinence rate of 5 per cent³. In older individuals the prevalence is reported to approach 60 per cent⁴. A number of independent factors are known to predict faecal incontinence^{1,3}. The social and

personal stigmas associated with the condition cause silent suffering and deterioration in quality of life. This is unfortunate in the presence of novel methods of treatment, some albeit still in an experimental stage.

Treatment of faecal incontinence requires a multi-disciplinary approach; surgical intervention is one of many therapeutic options. A comprehensive history and clinical examination in the initial assessment of patients is essential, but it is insufficient by itself^{5,6}, and must be supplemented by other special investigations. The use of anal manometry, pudendal nerve terminal motor latency, electromyography⁷, endoanal ultrasonography⁸, defaecography and proctography⁹ offers a better understanding of the problem and provides guidelines for deciding the optimal therapeutic approach. Patient selection is important to avoid disappointment¹⁰; only some forms of faecal incontinence are amenable to neosphincter reconstruction undertaken in

those who have failed to improve on conservative treatment or previously failed to benefit from sphincter or pelvic floor repair. In some who have lost of a large proportion of the native sphincter (after trauma or in congenital absence of sphincters), neosphincter reconstruction may be undertaken as a primary procedure. Patients should be prepared psychologically, emotionally and financially to undergo multiple operations with the possibility of being left with ultimate procedural failure¹¹ and a permanent stoma.

Surgical options

Surgical methods for treating faecal incontinence include either direct or overlapping sphincter repair for traumatic lesions, obstetric damage or iatrogenic sphincter injury in which pudendal nerve function is intact. Postanal repair or pelvic floor repair may be undertaken for anatomically intact but poorly functioning sphincters due to pudendal neuropathy. Long-term failure of such repairs has been estimated to be 86 per cent. This has led to the development of encirclement procedures for sphincter substitution^{12,13}. The principle of anal sphincter substitution involves the use of biological material or artificial mechanical devices to fashion a neosphincter around the non-functioning anal canal. Neoanal sphincter construction has also been carried out successfully after construction of a neorectum following proctocolectomy and abdominoperineal resection of the rectum^{14–16}; this has been termed total anorectal reconstruction.

The technique of gracilis muscle transposition was first described by Pickrell *et al.*¹⁷. This pioneering method of sphincter substitution was performed on 12 children who mostly had congenital causes of incontinence, such as spina bifida, meningocele or neurogenic malformation of the perineum and rectum. After undergoing this novel procedure all the children achieved satisfactory control of both faeces and gas. However, improvement of continence was not evaluated objectively by the authors by means of anorectal physiological studies. The procedure did not include the application of an electrical stimulus, which results in muscle fibre transformation^{18–26}. The lack of electrical stimulus may explain the poor initial results obtained with this method by other workers, which finally led to the decline in popularity of adynamic graciloplasty. Adynamic graciloplasty relied more on the muscle being wrapped tightly around the anal canal to cause some degree of mechanical obstruction that addressed only the retaining component of continence. Long-term follow-up of patients with gracilis muscle transposition revealed improved continence in a series of ten patients by Leguit *et al.*²⁷, but Keighley and co-workers had disappointing results^{28,29}. The later discovery of the possibility of improving fatigue

resistance in a muscle such as gracilis by electrical stimulation led to revival of muscle wrap techniques and the development of dynamic graciloplasty. The use of electrical stimulation to improve the function of the anal sphincters is not an entirely new concept. It was used with some success by Hopkinson and Lightwood^{30,31}, Caldwell^{32,33} and Glen³⁴. These workers mostly employed implanted electrodes or plug electrodes to stimulate the native anal sphincter directly. The overall efficacy of such methods in treating faecal incontinence was poor, possibly due to the denervated state of the anal sphincter that had undergone irreversible changes³⁵. This resulted in a temporary lack of further development of this technique.

Dynamic graciloplasty, pioneered by Baeten *et al.*³⁶ in Holland and by Williams *et al.*³⁷ in the UK, has proven to be effective in properly selected patients^{38–40} in whom other treatments have failed or are contraindicated⁴¹. Baeten *et al.* employed perineural electrical stimulation, whereas Williams *et al.* stimulated the gracilis muscle directly. Some authors have advocated the use of electrical stimulation only if adynamic graciloplasty has been unsuccessful⁴². Dynamic graciloplasty involves the release of the gracilis muscle from its distal attachment to the tibia (*Fig. 1*) and the creation of a muscle wrap around the native or artificially constructed anal canal in an α , γ or ϵ configuration, with attachment of the gracilis tendon to one of the ischial tuberosities^{37,43} (*Fig. 2*). Occasionally both gracilis muscles may be transposed around the anal canal in this fashion (double-wrap graciloplasty). The transposed muscle is then subjected to electrical stimulation to bring about the desired muscle fibre transformation from predominantly type II (fatiguable) to type I (fatigue resistant) muscle.

Physiology of striated muscle

Three distinct types of striated muscle can be distinguished, depending on ultrastructural, physiological and biochemical differences (*Table 1*). The main types are: (1) red, slow twitch (type I), (2) intermediate (type IIA) and (3) white, fast twitch (type IIB).

Red, slow twitch or type I muscle

Known as slow oxidative fibres that are predominant in slow contracting muscles (e.g. soleus and external anal sphincter), these muscles appear red even when exsanguinated because of their high content of the oxygen-storing pigment myoglobin. They can undergo prolonged repetitive contractions without fatigue. The sarcoplasm is rich in mitochondria and stains strongly for the oxidative enzymes of the Krebs cycle and the cytochrome oxidases. Morphologically, the fibres are narrow with thick Z and



Fig. 1 Graciloplasty. The gracilis muscle is mobilized along its length via two thigh incisions and an incision over the tibial tuberosity. The long saphenous vein and saphenous nerve are preserved. The blood supply to the middle part of the muscle is disconnected and the muscle is mobilized proximally up to the point of entry of the anterior obturator neurovascular bundle

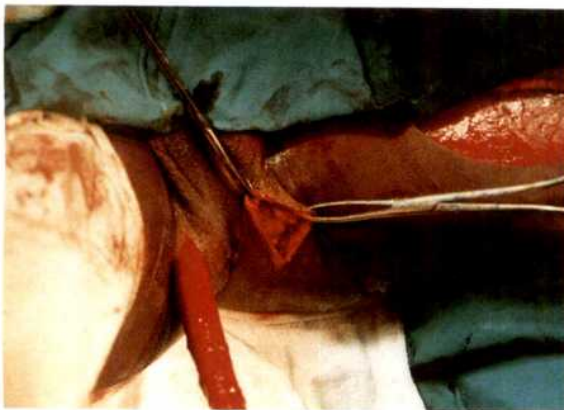


Fig. 2 Graciloplasty. The muscle is delivered into a circumanal tunnel through an incision in the deep fascia of the thigh, wrapped around the anal canal and attached to the contralateral ischial tuberosity

M bands, and have a staggered arrangement of sarcomeres. The glycogen content is high. The vascular supply is dense because of the high oxygen requirement of the muscle. The neuromuscular junctions tend to be less extensive than those of type II muscle fibres.

White, fast twitch or type II muscle

These muscle fibres are fast twitch and appear pale because of a reduced myoglobin content compared with slow twitch, type I fibres. Two subclasses have been identified: type IIA and type IIB. Type IIA fibres are known as fast glycolytic, oxidative or intermediate fibres. The muscle uses both glycolysis and oxidative phosphorylation for energy pro-

Table 1 Skeletal muscle types and their physicochemical properties

	Soleus	Gastrocnemius	Extraocular muscle
Characteristic	Type I	Type IIA	Type IIB
Myosin isoenzyme (ATPase) content	+	+++	+++
Sarcoplasmic reticulum Ca^{2+} pumping capacity	++	+++	+++
Diameter of myofibril	+ / ++	++	+++
Glycolytic capacity	+ / ++	+++	+++
Fatigue resistance	+++	++	+
Glycogen content	+	++	+++
Twitch speed	+	+++	+++
Myoglobin content	+++	+++	+
Capillary density	+++	+++	+
Type of respiration	Aerobic	Aerobic	Anaerobic

+, Low, slow or small; ++, intermediate; +++, fast, rapid or large. ATPase, adenosine 5'-triphosphatase

duction, hence the name intermediate fibres. These tend to have more mitochondria and to be more fatigue resistant than type IIB fibres. This type of muscle is uncommon in humans and primates but is found commonly in avian species. Type IIB fibres, known as fast glycolytic fibres, depend mainly on anaerobic glycolysis for energy production; these are less fatigue resistant^{44,45}.

Contractile properties of striated muscle

The physiological basis and characteristics of electrical and mechanical events in muscle are different. The depolarization of the muscle fibre membrane begins at the specialized structure at the end of the motor neurone (the motor endplate). The action potential that reaches the muscle through the motor endplate is transmitted along the muscle fibre and initiates muscle contraction. A single action potential causes a brief contraction of the muscle fibre, followed by relaxation, which is called a muscle twitch. The twitch begins about 2 ms after the commencement of membrane depolarization, before repolarization is complete. Type II muscle fibres have twitch durations as brief as 7.5 ms. However, the twitch duration of type I muscle fibres may be as long as 100 ms.

When a striated muscle is stimulated electrically, it remains refractory to further stimulation only during the rise and part of the falling phase of the spike potential, at which point muscle contraction commences. The contractile mechanism has no refractory period. This enables a second stimulus acting before full relaxation of muscle fibres to bring about additional activation of the contractile elements; this results in a response that is added to the

already persisting contraction. This is known as summation of contractions and results in the generation of tension far in excess of that generated during a single muscle twitch. If the muscle fibres are stimulated sufficiently rapidly, activation of the contractile elements occurs before any relaxation, and the individual responses fuse into a single, continuous contraction known as tetanic contraction or tetanization. During such a tetanic contraction the tension developed may be four times greater than that generated during individual muscle fibre contraction. The frequency of stimulation required to bring about tetanic contraction is determined by the twitch duration of the muscle. Generally, the required frequency is about ten times the twitch duration of the muscle fibre. These factors play an important role in determining the frequency of stimulation of transposed skeletal muscle.

Muscle fatigue

Sustained and strong contractions of striated muscle lead to the phenomenon of muscle fatigue, which plays a central role in the function of a transposed skeletal muscle neosphincter. The possible reasons for the development of muscle fatigue are depletion of muscle glycogen stores, depletion of creatine phosphate, decreased transmission at the neuromuscular junction, lack of nutrients such as oxygen necessary for muscle contraction, and accumulation of lactic acid caused by decreased blood flow to muscle. Development of fatigue in skeletal muscle motor units can be assessed by recording maximum stress maintained by the muscle during prolonged contraction or direct stimulation of the motor nerve to bring about a series of brief tetanic contractions. Muscle stress that is maintained during tetanic contraction rapidly decays to low levels which can be maintained for longer periods. This happens as a result of the early and almost complete failure of the type II motor units contained within the muscle. Muscle stress is then entirely maintained by the fatigue-resistant type I motor units^{44,45}.

Metabolism of skeletal muscle

Skeletal muscles derive energy mainly from three metabolic pathways: (1) anaerobic glycolysis, (2) oxidative phosphorylation and (3) direct phosphorylation via creatine phosphate and adenylate kinase.

Anaerobic glycolysis

This process takes place in the cytoplasm of the muscle fibre in the absence of oxygen. Glucose is split into two pyruvic acid molecules, simultaneously generating two molecules of

adenosine 5'-triphosphate (ATP). This is a relatively wasteful method of ATP generation, but the pyruvic acid so formed enters the next step in the cellular energy-producing mechanism in the mitochondria, namely the conversion of pyruvic acid to acetylcoenzyme A.

Oxidative phosphorylation

Acetylcoenzyme A undergoes further metabolism in the mitochondria in the presence of oxygen in the citric acid cycle (Krebs cycle). This involves oxidation of acetylcoenzyme A to carbon dioxide and water. This process of energy production in the mitochondria is known as oxidative phosphorylation, in which the hydrogen molecules generated in glycolysis and the Krebs cycle are split to yield hydrogen ions and electrons. These electrons then enter a series of electron acceptors lining the inner membrane of the mitochondrion that consist of ubiquinone, iron sulphide proteins and cytochromes B, C₁, C, A and A₃. The vast quantities of energy released in the process of electron transfer are used for the generation of ATP.

Direct phosphorylation

This involves an extremely rapid reaction in which adenosine 5'-diphosphate (ADP) is directly phosphorylated from creatine phosphate to generate ATP. This reaction takes place during the initial phase of muscular contraction until other energy systems become activated. The next direct phosphorylation reaction involves the transfer of a phosphate group from one ADP molecule to another to give rise to ATP and adenosine 5'-monophosphate (AMP). This is an important step in myofibril energy synthesis as the ADP and AMP formed in the activation of muscle contraction stimulate the rate-limiting enzyme in glycolysis, phosphofructokinase, and drives the myofibrillary energy-producing mechanism forwards⁴⁴.

Electrical stimulation and its impact on skeletal muscle

The purpose of neoanal sphincter construction is to achieve anal canal closure, usually a function of the internal anal sphincter, and to maintain voluntary closure of the anal canal, a function of the striated muscle component. Low-frequency electrical stimulation converts type II muscle fibres, found in the gracilis, to type I muscle fibres which are fatigue resistant and thus simulate internal anal sphincter function. This process has been studied extensively in a number of animal models^{18-20,24,46-48} and in humans^{49,50}. The concept of electrical transformation of skeletal muscle has also been used with success in improving the function of

the failing myocardium. This was achieved by using converted and synchronously paced latissimus dorsi muscle to replace resected myocardium⁵¹.

Fibre-type conversion

In the rat, chronic low-frequency stimulation of a 'fast' muscle brings about conversion of the fast muscle fibres to a 'slow' type, with an increase in both fatigue resistance and capillary density¹⁸. Lack of change in the physical properties of the muscle, such as twitch duration in the rat and guinea-pig (not seen in some other species such as rabbit), suggests interspecies differences in transformation of fast to slow muscle by electrical stimulation^{18,25}. This may be important in correlating data obtained from animal studies to clinical situations.

Stimulation of 'fast' muscle types, such as extensor digitorum longus (EDL), with electrical stimulation resembling the normal firing pattern of a slow muscle, such as soleus, in the rat brings about a moderate change in fibre types, Ca²⁺ sequestering proteins (parvalbumin, sarcoplasmic reticular Ca²⁺ ATPase), enzymes of energy metabolism and lactate dehydrogenase of the EDL to resemble that of the soleus^{21,22}. Denervation of a slow muscle such as soleus and subjecting it to chronic high-frequency electrical stimulation results in a decrease in isometric twitch duration and an increase in maximum isotonic shortening velocity comparable to that of a typically 'fast' muscle such as EDL. The fast stimulated soleus labels strongly with antibodies against fast myosin and weakly with antibodies against slow myosin, confirming the transformation of 'slow' to 'fast' myosin types²³. Williams and colleagues used continuous low-frequency stimulation to transform sartorius muscle fibres from type II to I, and fashioned the muscle in the form of a sphincter around a loop of ileum (Thiry-Vella loop) in a canine model³⁵.

Histological and physiological changes in stimulated skeletal muscle

Changes following chronic low-frequency stimulation of type II skeletal muscle fibres consist of the following:

- 1 decrease in contractile speed
- 2 general increase in muscle fibre diameter⁴⁹ and loss of uniformity in size, shape and staining intensity of muscle fibres with fatty infiltration and marked thickening of connective tissue septae³⁵
- 3 lower fusion frequency for tetanic contraction^{39,49}
- 4 altered kinetics of release and uptake of Ca²⁺ in muscle fibres

- 5 decrease in T tubule system and sarcoplasmic reticulum
- 6 switch from anaerobic glycolysis to oxidative phosphorylation
- 7 increase in capillary density³⁵
- 8 increase in mitochondrial content³⁵
- 9 alteration in light and heavy myosin isomers to those characteristic of slow muscle type; this transformation occurs sequentially in the order IIB → IIX → IIA → I^{26,52}.

Blood supply of the gracilis muscle

The gracilis has an abundant arterial supply that reaches the deep aspect of the muscle through a proximal and distal pedicle. The majority of the blood supply (73 per cent) is from the branches of the profunda femoris artery, supplying the adductors of the thigh, and a lesser proportion of muscle blood supply arises from the medial circumflex femoral artery⁵³. Furthermore, studies have shown that proximal blood supply plays a dominant role⁵⁴, although in a proportion of patients both proximal and distal vascular supply have clear demarcations and these are interconnected by variable intramuscular vascular anastomoses. It seems likely that patients with a dominant proximal pedicle and poor intramuscular anastomoses between proximal and distal pedicles will have ischaemia of the distal muscle when transposition is undertaken without a vascular delay procedure³⁷. Still, several studies have shown little benefit from employing a vascular delay procedure^{55,56}. Electrical stimulation may also have an impact on muscle blood flow; stimulation of canine gracilis at a frequency of 5 Hz has been shown to increase both intramuscular pressure and total blood flow, while stimulation at 100 Hz produced a reduction in total blood flow and consequently ischaemia⁵⁷. It is unclear from the human studies performed so far whether early electrical stimulation results in ischaemia of the gracilis muscle.

Alternatives to gracilis

Alternatives have been sought that may be used when the gracilis is unavailable or unsuitable. The vascular and nerve supply of semitendinosus and long head of biceps femoris have been studied in human cadavers⁵⁸. The long head of the biceps femoris receives its blood supply from the first and second perforating arteries and its nerve supply from a motor branch of the sciatic nerve. The semitendinosus, however, receives its dominant blood supply from the medial circumflex femoral artery in proximity to the ischial tuberosity and the second perforating artery. It receives its nerve supply from two motor branches of the sciatic nerve. Reinnervation of a fast muscle by a nerve supplying a slow muscle has the expected adaptive effect⁴⁹. Congilosi *et al.*⁵⁹

reported satisfactory results after innervating transposed skeletal muscle with the pudendal nerve over electrically stimulated muscle wraps in maintaining continence in a canine model.

Frequency and type of muscle stimulation

The optimal frequency, pattern and duration of muscle stimulation has been shown to be 10 Hz continuously for 6 weeks in the rabbit⁴⁶. Muscle stimulation parameters have not been properly determined in humans, but chronic stimulation has been shown to be more effective in bringing about muscle-type transformation than intermittent stimulation⁶⁰. Stimulation of skeletal muscle with a background low-frequency current, coupled with intermittent short bursts of high frequency of the order of 100 Hz, causes muscle transformation with preservation of muscle mass. Loss of muscle mass and reduction in the pressure-generating capacity of the neosphincter has been observed by some⁴⁹. However, muscle atrophy can be minimized by ensuring an adequate degree of stretch of the gracilis muscle during neosphincter reconstruction⁶¹. The overall effect is to transform the functional characteristics of type II muscle to that of type I muscle. Immediate commencement of electrical stimulation after transposition gives more desirable changes in the muscle⁵⁵. Cessation of electrical stimulation causes a reversal in the muscle fibre type, from type I to type II, emphasizing the importance of continuous electrical stimulation^{40,42,49,60}. Stimulation of the main nerve to gracilis and not its peripheral branches ensures contraction of the whole muscle and not a part of it. This reduces the voltage that is necessary to achieve stimulation³⁷. However, Wexner and colleagues have shown that improvement in continence is significantly greater in patients who receive intramuscular perineural stimulation of the gracilis than in those in whom only the main trunk of the nerve to the gracilis is stimulated⁶².

Muscles used in construction of neoanal sphincters

The gracilis has been by far the most frequently used muscle in neoanal sphincter construction. It is slender, flat and is found superficially in the medial aspect of the thigh. The muscle is broad and fleshy at its origin, becoming thin as it tapers down to a rounded tendon close to its insertion. Proximal attachment is to the medial half of the lower part of the body of the pubic bone, inferior pubic ramus and corresponding ischial ramus. It then descends on the medial aspect of the thigh and its distal rounded tendon crosses the medial femoral condyle, posterior to the insertion of the sartorius, to be inserted on to the medial tibial metaphyseal

surface slightly distal to its condyle, between the insertion of the sartorius anteriorly and semitendinosus posteriorly. Appreciation of this relationship is important in identifying the gracilis muscle at operation. The muscle is supplied by motor branches from the anterior division of the obturator nerve (L₂, L₃). The advantage of using the gracilis as a neosphincter is that its loss does not result in a functional deficit in the lower limb after transposition⁶³. The use of two gracilis muscles may be an advantage. In the event of initial neosphincter function failure, the vascular supply of the semitendinosus muscle can provide a suitable arc of rotation for transposition around the anus⁶⁴, which makes this latter muscle more suitable than the gracilis for transposition. Furthermore, Williams and co-workers revealed that the long head of biceps femoris also has anatomical characteristics that make it a suitable alternative to the gracilis⁶⁵. However, both muscles are flexors of the knee joint and their loss is likely to impair knee joint movement and stability.

Other substitutes that have been used to encircle the anal canal are the gluteus maximus, either singly^{66–68} or as a bilateral wrap^{69–71}, and the obturator internus muscle⁷². Transposed glutei may allow easier contraction than gracilis as the former are natural synergists of the anal sphincter⁷³ and the glutei play an auxiliary role in maintaining continence⁷⁴. However, the functional deficit after gluteal transposition may be more than that after graciloplasty. The operation itself is technically more complicated as both glutei must encircle the anal canal⁷¹. The palmaris longus muscle of the hand has also been used as a free muscle graft, but without much of an impact on continence⁷⁵.

Results of gracilis muscle transposition

The chief reason for the use of gracilis muscle transposition as a neosphincter has been either to replace a neuropathic or absent native anal sphincter or to augment partial anal sphincter loss when direct or overlapping anal sphincteroplasty is not possible. In neuropathic anal sphincter injury, such as after prolonged labour, postanal repair⁷⁶ or total pelvic floor repair must be attempted before considering patients for a neosphincter⁷⁷.

The results of gracilis muscle stimulation are summarized in Table 2. Although Pickrell *et al.*¹⁷ and others have reported satisfactory results from an unstimulated single- or double-wrap graciloplasty, the addition of stimulation is likely to provide a better quality of continence by improving resting anal pressures. Despite reports of improvement in continence after graciloplasty in several series, it has not been possible directly to compare reported studies because of variation in selection criteria, technique of stimulation,

Table 2 Summary of results after graciloplasty

Reference	Year	No. of patients	Length of follow-up	Adynamic or dynamic	Outcome
Pickrell <i>et al.</i> ¹⁷	1954	12	5 years*	Adynamic	Improved continence 100%
Corman ⁷⁸	1985	14	60–107 months	Adynamic	Improved continence 79% Failure rate 21%
Leguit <i>et al.</i> ²⁷	1985	10	6 months to 17 years	Adynamic	Improved continence 90% Failure rate 10%
Yoshoka and Keighley ²⁸	1988	6	NS	Adynamic	Failure rate 100%
Christiansen <i>et al.</i> ³⁸	1990	13	NS	Adynamic	Improved continence 83% Failure rate 17%
Cavina <i>et al.</i> ⁷⁹	1990	47	NS	Dynamic	Improved continence 88% Failure rate 12%
Williams <i>et al.</i> ⁶⁰	1990	6	NS	Dynamic	Improved continence 83% Failure rate 17%
Sonnino <i>et al.</i> ⁸¹	1991	7	0.5–12.5 years/4.4 years†	Dynamic	Improved continence 100%
Konsten <i>et al.</i> ⁶²	1992	12	16 months to 5 years	Dynamic	Improved continence 67% Failure rate 25%
Konsten <i>et al.</i> ⁸³	1993	26	NS	Dynamic	Improved continence 77% Failure rate 23%
Baeten <i>et al.</i> ⁴¹	1994	9	NS	Dynamic	Improved continence 56% Failure rate 44%
Faucheron <i>et al.</i> ⁴²	1994	22	6 months*	Adynamic followed by electrostimulation in six patients	Adynamic: improved continence 81%; failure rate 19% Dynamic: improved continence 67%; failure rate 23%
Korsgen and Keighley ²⁹	1995	4	NS	Dynamic	Failure rate 100%
Baeten <i>et al.</i> ³⁶	1991	52	2.1 years‡	Dynamic	Improved continence 73% Failure rate 27%
Cavina ⁸⁴	1996	81	78.6 months†	Dynamic	Improved continence 90% Failure rate 10%
Geerdes <i>et al.</i> ¹⁰	1996	67	2.7 years†	Dynamic	Improved continence 78% Failure rate 22%
Wexner <i>et al.</i> ¹¹	1996	17	NS	Dynamic	Improved continence 60% Failure rate 40%
Mander <i>et al.</i> ¹⁵	1996	12	1 year*	Dynamic	Improved continence 67% Failure rate 33%
Sieleznoff <i>et al.</i> ⁸⁵	1996	8	48.5 months*	Adynamic	Improved continence 100%
Wexner <i>et al.</i> ⁸⁶	1996	14	NS	Dynamic	Improved continence 60% Failure rate 40%
Geerdes <i>et al.</i> ¹⁶	1997	20 (15 evaluated)	1–60 months 24 months†	Dynamic	Improved continence 53% Failure rate 13%
Altomare <i>et al.</i> ⁸⁷	1997	9 (5 evaluated)	NS	Dynamic	Improved continence 80% Failure rate 20%
Baeten and Rongen ⁸⁸	1997	21	NS	Dynamic	Improved continence 52% Failure rate 48%
Christiansen <i>et al.</i> ⁸⁹	1998	13	7–27 months	Dynamic	Improved continence 85% Failure rate 15%
Cavina <i>et al.</i> ⁹⁰	1998	31 (26 evaluated)	37.8 months†	Dynamic	Improved continence 85% Failure rate 15%
Rosen <i>et al.</i> ⁹¹	1998	28	NS	Dynamic	Improved continence 90% Failure rate 10%
Cavina <i>et al.</i> ⁹²	1998	98 (61 evaluated)	55 months‡	Dynamic	Improved continence: 87% after chronic nerve stimulation; 69% after short-term nerve stimulation
Rullier <i>et al.</i> ⁹³	1998	10 (7 evaluated)	16 months†	Dynamic	Improved continence 86% Failure rate 14%
Sieleznoff <i>et al.</i> ⁹⁴	1999	18 (16 evaluated)	20 months†	Dynamic	Improved continence 81% Failure rate 19%
Rongen <i>et al.</i> ⁹⁵	1999	7	1.1–34.8 years 8.5 years†	Dynamic	Improved continence 71% Failure rate 29%
Ruoanet <i>et al.</i> ⁹⁶	1999	9 (7 evaluated)	14–50 months 32 months†	Dynamic	Improved continence 71% Failure rate 29%

*Maximum, †mean, ‡median period of follow-up. NS, not stated

stimulation protocols and stimulators. Furthermore, authors have used different continence scoring criteria with varying periods of follow-up. Achievement of a successful outcome after gracilis muscle transposition requires trained surgeons, facilities for anorectal physiology testing and sphincter imaging, technical support for stimulators and stimulator protocols, stoma therapists and, preferably, persons trained in biofeedback techniques. The authors consider that the operation should be confined to specialist centres.

Complications of electrostimulated graciloplasty

Electrical stimulation of transposed skeletal muscle is associated with a number of specific complications. The three main groups of complications are technical, infectious and physiological¹⁰ (Table 3). Technical complications and complications associated with infection may be prevented or treated, with good results. However, physiological complications associated with impaired sensation or motility are more difficult to rectify. Specifically, patients who undergo graciloplasty for incontinence are likely to have a better outcome than those who have graciloplasty as part of total anorectal reconstruction, because the latter group of patients will have lost their sense of impending evacuation as a result of removal of the anal canal. Development of perineal skin-inverting techniques during anorectal reconstruction, and artificial anal sensory feedback systems, may help improve continence in this group of patients. Furthermore, replacement of the native rectum with a straight colonic tube neorectum or a colonic pouch during total anorectal reconstruction has been associated with disorders of frequent defaecation and pouch motility respectively. Yet another functional disorder after gracilis muscle transposition has been difficult evacuation. Evacuation difficulty may also be encountered after sphincteroplasty and other forms of pelvic floor repair for faecal incontinence. Probable causes include tight muscle

encirclement, pelvic floor incoordination, fibrosis at the site of repair, and an 'hour glass' effect of the neorectum as it traverses the pelvic floor.

Artificial bowel sphincters

Artificial sphincters have been used in the treatment of urinary incontinence for more than 25 years with a success rate of 90 per cent⁹⁷. Initial attempts at using a urinary prosthesis in the management of faecal incontinence resulted in success rates of up to 73 per cent⁹⁸, comparable to the results obtained from dynamic graciloplasty. The indications for artificial sphincter placement are usually the same as those for biological neosphincters. Additionally, artificial sphincters are useful in managing faecal incontinence of neuromuscular origin, such as myasthenia gravis⁹⁹ or diabetic neuropathy. Infection is a problem that requires removal of the prosthesis, and the results of longer follow-up are required before making any stronger recommendation for the use of such sphincters.

The modified artificial bowel sphincter consists of a silicone rubber cuff that is between 9 and 12 cm long and 2 cm wide; it is used to encircle the anal canal (Fig. 3). The cuff is connected to a water-filled balloon reservoir, usually situated in the subperitoneal space in the retropubic area, and a control pump situated in an accessible site such as the scrotum in men and the labium majus in women. The balloon reservoir is capable of maintaining a constant pressure in the entire system, which is able to generate a cuff closing pressure of up to 90 cmH₂O. In studies with a follow-up of up to 40 months, it has been shown that continence of solid may be achieved in almost all patients, but continence of gas was possible in only 50 per cent^{100–102}.

Quality of life is reported to improve after implantation of the artificial anal sphincter in over 90 per cent of patients¹⁰². However, incomplete evacuation of the rectum is a problem for a minority^{101,102}. Perianal infection and mechanical failure of one of the components of the artificial sphincter are significant difficulties that require removal of

Table 3 Complications associated with electrical stimulation of transposed skeletal muscle

Technical	Infectious	Physiological
Fibrosis around electrode	Infection of the lead	Overflow incontinence
Displacement of electrode and/or stimulator	Infection around stimulator	Soiling
Fracture of lead	Perianal infection	Non-distending rectum
Short battery life of stimulator	Infection and cellulitis of the thigh wound	Strong peristalsis
Poor contraction of distal muscle		Severe constipation
Perforation of anal canal		
Inability to stimulate transposed muscle		
Loose anal wrap		

Table 4 Results of studies with the artificial bowel sphincter

Reference	No. of patients	Follow-up (months)	Continence for solids	Continence for gas	Impaired evacuation	Infection	Explanation of sphincter
Wong <i>et al.</i> ¹⁰⁰	9	40	7	4	—	3	1
Christiansen and Lorentzen ⁹⁹	10	6	10	4	2	2	2
Lehur <i>et al.</i> ¹⁰²	10	20	10	5	3	2	1
O'Brien and Skinner ¹⁰³	9	6	8	—	—	1	2
Finlay <i>et al.</i> ¹⁰⁴	8	16	6	—	2	1	2

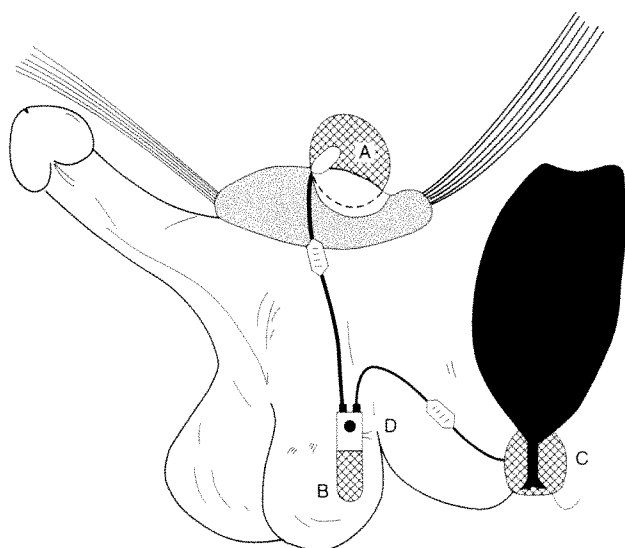


Fig. 3 Representation of the artificial anal sphincter to show its components. (A) Water-filled balloon reservoir situated in the retroperitoneal space. (B) Manually operated pressure pump which enables movement of fluid between the reservoir (A) and the anal sphincter cuff (C). (C) Cuff device that occludes the anal canal when filled with water. (D) Deactivation button which enables disconnection of the fluid column between the reservoir (A) and the cuff (C)

the prosthesis (Table 4). In a recent study, Finlay *et al.*¹⁰⁴ employed a rather different style of artificial anal sphincter (GS2000, prototype), which is implanted around the anorectum just above the level of the puborectalis muscle at laparotomy. These authors claim that cuff closure is achieved at a lower pressure than with the type of bowel sphincter shown in Fig. 3 (AMS800, Acticon®, Pfizer-American Medical Systems, Minneapolis, MN, USA), thus preventing ischaemia at the site of cuff closure. Two of eight patients in their series required removal of the prosthesis; one because of infection and the other because of pseudomembranous colitis. The authors noted that such a low-pressure closure device provided continence only for solid stool and not for liquid stool. The artificial bowel

sphincter is less costly than dynamic graciloplasty, offers the surgeon a technically easier implantation procedure and gives the patient immediate continence, unlike a muscle transposition which requires prolonged stimulation¹⁰².

Conclusion

Fibre-type conversion resulting in fatigue resistance is the chief reason for the choice of electrostimulated biological neosphincter construction in patients with end-stage faecal incontinence. The artificial sphincter appears to be a viable, less expensive alternative. Reports of both procedures claim improved continence in the majority of patients. However, both types of neosphincter operation are associated with morbidity; postoperative infection and impaired evacuation are predominant. Addition of antegrade irrigation via a Malone stoma¹⁰⁵ or colonic conduit¹⁰⁶ may result in fewer conversions to a permanent stoma. Further studies are required to ascertain the role of biofeedback in the management of biological neosphincters¹⁰⁷.

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Biological behaviour and clinical implications of micrometastases

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Background: The most important prognostic determinant in cancer is the identification of disseminated tumour burden (metastases). Micrometastases are microscopic (smaller than 2 mm) deposits of malignant cells that are segregated spatially from the primary tumour and depend on neovascular formation (angiogenesis) to propagate.

Methods: The electronic literature (1966 to present) on micrometastases and their implications in malignant melanoma and epithelial cancers was reviewed.

Results: Immunohistochemical techniques combined with serial sectioning offer the best accuracy for detection of nodal micrometastases. Molecular techniques should be reserved for blood samples or bone marrow aspirates. Detection of micrometastases in regional lymph nodes and/or bone marrow confers a poor prognosis in epithelial cancers. The concept of sentinel node biopsy combined with serial sectioning and dedicated screening for micrometastases may improve staging procedures. Strategies against angiogenesis may provide novel therapies to induce and maintain micrometastatic dormancy.

Conclusion: The concept of micrometastases has resulted in a paradigm shift in the staging of epithelial tumours and our overall understanding of malignant processes.

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Introduction

A micrometastasis is a microscopic (smaller than 2 mm) deposit of malignant cells distinct from the primary lesion^{1,2}. Its potential capacity to evade immune surveillance, invade vascular channels and develop into macroscopic disease has led to considerable focus on the micrometastatic concept³. The detection of micrometastases in a variety of anatomical locations has resulted in an 'upstaging' of tumours and the incorporation of micrometastatic disease into the tumour node metastasis staging system^{4–7}.

Identification of micrometastatic cells can be problematic owing to varying sensitivity and specificity of detection methods. For example, necrotic cells shed from a tumour may be detectable in regional lymph nodes but they are non-viable and so not micrometastatic⁸. In contrast, systemic tumour cell dissemination detected in bone marrow holds a stronger association with outcome since cells of epithelial origin are not present in bone marrow under normal conditions^{5,9,10}. Bone marrow samples acquired before surgical manipulation of the primary tumour offer the best

indication of systemic micrometastatic disease and stage of neoplastic spread^{5,10}. This method of assessment is used increasingly as a staging technique in epithelial cancers where micrometastases largely correlate with prognosis.

Any proposal to treat micrometastases must first clarify which detection methods should be used to identify these malignant cells. It is also essential to understand the process(es) whereby these cells transform into overt macrometastatic disease and the mechanisms involved, including angiogenesis. This review focuses on these topics for malignant melanoma and epithelial cancers.

Angiogenesis and micrometastatic behaviour

A fundamental biological characteristic of micrometastases which distinguishes them from macroscopic cancer is the absence of a specific blood supply. Therefore, micrometastatic cells are dependent on passive diffusion for oxygen and nutrient supply, and this may limit their growth to 2–3 mm^{1,11,12}. These cancer cells may remain in a dormant state for long periods during which cytokinetic and apoptotic rates are matched such that there is no net

growth. An equilibrium exists until they are detected and eradicated by immune surveillance, or they acquire a blood supply that permits growth, invasion of vascular channels and distant spread^{13,14}. This process of neovascular acquisition, termed angiogenesis, is an active process that requires degradation of the extracellular matrix, endothelial cell proliferation, migration and neotubule formation. Among the stimuli for angiogenesis that have been identified, the most important are hypoxia and inflammatory mediators¹³. Thus the balance between dormancy and neovascular progression is dependent on angiogenic stimuli and apoptotic rates¹⁴. The ratio of these processes controls the characteristics of the dormant malignant cells.

The biologically active molecules involved in the angiogenic cascade have been reviewed recently¹³. Vascular endothelial growth factor (VEGF) is a major angiogenic stimulant with four homodimeric isoforms identified to date¹⁵. VEGF expression and secretion is stimulated by hypoxia, mechanical stretch and stress-induced cytokines^{16,17}. It serves as a chemotactic and mitogenic stimulus to vascular and lymphatic endothelium, and plays a key role in the initial degradation of the extracellular matrix¹⁸. Moreover, VEGF enhances local expression of tissue plasminogen activator, urokinase plasminogen activator (uPA), endothelial cell uPA receptor and integrins (e.g. $\alpha v \beta 3$ and $\alpha v \beta 5$)^{19–21}. VEGF overexpression in tumours is associated with a metastatic phenotype and correlates with a poor prognosis^{22–25}. VEGF is expressed selectively in some tumour cells compared with adjacent endothelial cells^{22,23,26}. However, the latter may overexpress messenger RNA (mRNA) for VEGF receptor isoforms (e.g. *flt-1* and *KDR*) in tumours²³. Therefore, the VEGF receptor complex has been proposed as a target for therapies designed to ablate tumour-associated endothelium²⁵.

The fibroblast growth factor (FGF) family, of which nine different members have been identified, is another group of potent angiogenic cytokines¹³. Basic FGF (bFGF) is produced by vascular smooth muscle cells, endothelial cells, fibroblasts, monocytes and macrophages²⁷. Among its effects, bFGF upregulates uPA and $\alpha v \beta 3$ integrin expression, thereby encouraging endothelial cell migration and tubule formation^{21,28}. Four FGF receptor isoforms exist and are expressed in a cell- and tissue-specific fashion²⁹. bFGF is instrumental in wound healing (including gastroduodenal ulcers) and tissue responses to ischaemia, as well as stimulating tumour angiogenesis^{30–34}. In addition, a synergistic relationship exists between proangiogenic cytokines, since VEGF synthesis is stimulated by bFGF and other growth factors in tumours³⁵.

The stimulatory effect of trauma on angiogenesis may explain why dormant metastatic tumour cells proliferate

following a surgical insult delivered from months to years after the resection of primary disease. The signal for this appears to be angiogenic peptide factors released in response to wounding at the primary or secondary surgical insult^{36–39}. Furthermore, enhanced postoperative angiogenesis and micrometastatic proliferation may be due to resection of the primary tumour and removal of its inhibitory influence. For example, following cytoreductive surgery micrometastases are maintained in a dormant state if they are exposed to serum from tumour-bearing mice³⁶. As a result of this finding several endogenous antiangiogenic plasma factors have been identified^{36–39}. The plasminogen fragment angiostatin inhibits neovascularization and metastatic progression^{36,37}. Systemic administration of angiostatin and human plasminogen fragments inhibits angiogenesis and growth of metastases in murine models^{36,37}. Endostatin, a fragment of collagen XVIII, acts as a potent inhibitor of endothelial proliferation, angiogenesis and tumour growth³⁸. Micrometastases exhibit a threefold increase in apoptotic rates when treated with angiogenic inhibitors^{11,37}. Therefore, it is hoped that the success of antiangiogenic strategies against VEGF and bFGF *in vitro* and *in vivo* will extend to clinical practice^{40–43}.

Detection of lymph node micrometastases

Identification of lymph node metastases represents an integral component of tumour staging. Nodal status determines prognosis in epithelial malignancies and governs the indications for adjuvant therapy⁴⁴. Traditional pathological staging involved single or double sectioning of nodes sampled from cancer specimens. The potential inaccuracy of this practice may understage patients owing to missed nodal disease outside the histological field^{44–47}. The concept of sentinel lymph node biopsy emerged in an effort to localize the first draining node of a tumour site such that more accurate but less invasive histological staging is facilitated^{45–47}.

Sentinel lymph node biopsy

Lymphatic afferents from a primary tumour drain into a single focus, termed the sentinel node(s), before drainage into the regional lymphatic basin⁴⁵. Localization of this lymph node, with vital dyes and/or radiolabelled colloid injected at the site of or into the primary lesion, permits focused evaluation for metastatic cells⁴⁵. Sentinel lymph node biopsy facilitates detailed pathological examination for micrometastatic deposits because of the small tissue volume. This technique reduces the morbidity of nodal acquisition and may obviate formal lymph node dissection in patients with negative sentinel nodes^{45–47}. A recent

multicentre study has confirmed the accuracy of sentinel node biopsy in predicting nodal metastases, although an initial learning curve of 30 cases exists⁴⁷. Accurate identification of metastatic cells in the sentinel node is crucial; the node is divided into multiple sections that are submitted to rigorous examination⁴⁷. There are three available options for localization of nodal micrometastases: haematoxylin and eosin staining with light microscopy, immunohistochemical analysis using specific antibodies and molecular techniques.

Haematoxylin and eosin staining

Haematoxylin and eosin is commonly used for lymph node staining in malignant disease, with characteristic metastatic features defined at light microscopy. However, small foci may be missed owing to inadequate sectioning of the node⁴⁸. A recent recommendation is that lymph nodes be sectioned at least three times for examination to improve detection of micrometastases⁴⁸.

Immunohistochemistry

Cytokeratin proteins, which form an essential constituent of the cytoskeleton in both normal and malignant epithelial cells, serve as reliable markers for identifying the epithelial origin of localized cells⁴⁹. Therefore, epithelial cells may be detected in lymph nodes using specific anticytokeratin antibodies and immunostaining. Several studies have shown this to be a valuable technique in detecting micrometastases because it has a far superior sensitivity to haematoxylin and eosin staining alone^{50–52}. A correlation between micrometastasis positivity of lymph nodes and decreased post-operative survival in upper gastrointestinal and breast malignancy has been identified using cytokeratin localization^{53,54}.

Immunostaining allows any epithelial-specific antigen to be stained where a corresponding antibody exists. The oncoprotein P53 has been used successfully as a target for immunohistochemical staining of primary specimens and nodes taken at radical pulmonary resection for non-small cell carcinoma⁶. Micrometastases were identified in 45 per cent of lymph nodes that were judged to be negative for metastatic disease using standard techniques in this study⁶. Micrometastatic positivity also conferred a significantly worse prognosis compared with that of true lymph node-negative patients.

Molecular techniques

The introduction of molecular biology to applications in clinical practice has led to an impetus for its use in the

detection of nodal micrometastases^{55–59}. Tumour cells may produce specific proteins that differentiate them from normal. The expression of the specific genes coding for these proteins can be detected and amplified by reverse transcriptase–polymerase chain reaction (RT-PCR) in order to detect tumour cells. This technique was used initially in the identification of neuroblastoma with neuroendocrine gene 9.5 (PGP 9.5) and malignant melanoma using the tyrosinase gene^{7,60}. Localization of carcinoembryonic antigen (CEA), a marker for gastrointestinal carcinoma, by this technique may identify ectopic CEA-positive cells^{51,61,62}. However, this highly sensitive method of detecting micrometastases is limited by concern about high false-positive rates since nodal contamination by DNA from shed, non-viable tumour cells may result in an inappropriate labelling of micrometastases⁸. Mutant-allele-specific amplification (MASA) is a PCR-based assay for amplification of tumour-specific DNA sequences which may detect a tumour cell in a background of thousands of cells⁶³. MASA is capable of detecting micrometastases in lymph nodes that are classified as histologically negative⁶⁴. MASA-detected tumour cells in lymph nodes correlate with an increase in local recurrence rates in patients with colorectal carcinoma⁶⁵.

Methods of increasing nodal yield

A number of methods have been described of increasing the yield of lymph nodes retrieved at formal dissection in an attempt to improve the accuracy of metastatic detection^{66–68}. Xylene alcohol clearance increases the nodal yield from colorectal carcinoma specimens but does not alter staging⁶⁶. In radioimmunoguided surgery, a radiolabelled cytokeratin antibody is injected before operation and a γ radiation probe is used peroperatively to detect occult metastatic disease. Such localization combined with increased sectioning increases the detection of nodal micrometastases^{66,68}. However, the specificity of this process is disappointing as up to one-third of nodes identified as positive have no evidence of micrometastasis on immunohistochemical analysis^{66,68}.

Detection of micrometastases in bone marrow

The bone marrow cavity provides an accessible space not normally contaminated with epithelial cells; its native cells are mesenchymal in origin and easily distinguished from malignant epithelial cells by a variety of techniques⁶⁹. The methods commonly used are immunocytochemistry, flow cytometry and molecular techniques (RT-PCR). Detection of bone marrow micrometastases is a predictor of poor prognosis in patients with epithelial malignancies, includ-

ing breast, lung and colorectal cancer^{70,71}. Bone marrow micrometastases are present in over one-quarter of patients undergoing 'curative' resection of gastrointestinal cancer^{72,73}. Whether these occult deposits of metastatic cells have biological significance or if they reflect the behaviour of the primary tumour remains to be determined. There is additional uncertainty about the viability and longevity of these micrometastatic cells, although persistence of marrow micrometastases up to 6 months after operation suggests that they reflect minimal residual disease in some patients undergoing 'curative' surgical resection^{72,73}. Thus, micrometastases present an opportunity to study the metastatic process and the related issue of tumour dormancy⁷³.

Immunohistochemistry

Initial studies on breast and colorectal bone marrow micrometastases using an anticytokeratin antibody failed to demonstrate a correlation with distant metastatic disease^{69,74}. However, the presence of micrometastases was found to be positively associated with pathological tumour stage. There is much debate in the literature on the significance of micrometastases detected using immunocytochemistry alone^{70,72-76}. One meta-analysis of studies on bone marrow micrometastases detected by this technique failed to show a correlation between such micrometastases and relapse-free survival time; only in breast cancer was the relative risk for reduced survival associated with bone marrow positivity for micrometastases⁷⁷.

Flow cytometry

Micrometastases may not be uniformly distributed throughout the body or in the bone marrow cavity and it is probable therefore that sampling errors (false negatives) occur. The inherent inaccuracy and lack of quantitative information with conventional immunohistochemical techniques has led to the development of an automated process in which a laser detects fluorescein-conjugated antibodies bound to cytokeratin epitopes on micrometastases^{72,73}. This flow cytometric analysis of immunocytochemically stained marrow facilitates rapid processing of samples and more accurate enumeration of tumour cells^{72,73,78}. The sensitivity of flow cytometric analysis is ten or fewer neoplastic cells per 10⁵ marrow cells⁷².

Molecular techniques

Molecular methods of detecting occult metastatic cells in bone marrow have also been explored in an attempt to improve overall sensitivity and specificity. The detection of mRNA for a specific marker protein by PCR is a highly

sensitive approach to micrometastatic tumour detection. One of the main criticisms of RT-PCR is that the oversensitivity of the technique, which increases with the number of amplification cycles, results in false-positive results either because of contamination or illegitimate transcription. For example, cytokeratin (CK) 18 pseudogenes have been found in normal marrow and CK20 can be demonstrated in granulocytes^{79,80}. The term pseudogene is used because it refers to a non-functional gene that can artificially transcribe CK18 complementary DNA. However, RT-PCR techniques directed at CEA detection in haemopoietic bone marrow samples have been reported accurately to detect single cells in 2 × 10⁷ bone marrow cells, with low false-negative rates and a greater sensitivity than immunohistochemistry⁸¹. Similarly, tyrosinase RT-PCR detects ten or more tumour cells per millilitre of whole blood^{7,81}. RT-PCR techniques may prove useful for detection of bone marrow micrometastases in patients with colorectal cancer using CK20⁸². Over one-third of patients in this study were deemed positive and this correlated with the stage of the primary tumour. Future studies will clarify the significance of bone marrow micrometastases detected by RT-PCR and the optimal techniques to improve specificity.

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) has recently been used in the detection of CK19 in bone marrow aspirates from patients with breast, stomach and colorectal cancers⁸³. The technique involves lysis of the nucleated cell component of the marrow sample, application of monoclonal antibodies to epitopes of CK19, and concentration determination by optical methods with comparison to a standard curve. Significant concordance between ELISA for CK19 and immunohistochemical analysis for CK18 was found in this patient population⁸⁴. ELISA offers advantages over immunohistochemistry in that it permits more rapid assessment and reduces observer bias. However, the accuracy of ELISA relies heavily on the specificity of the antibodies used and it is likely that it will be superseded by techniques based on molecular biology.

Detection of bloodborne micrometastases

There is little known about the prognostic significance of tumour cells in the circulating bloodstream. Molecular techniques such as MASA have been used to detect the relatively small number of cells found in peripheral blood⁸⁵. It is proposed that few shed tumour cells in the bloodstream succeed in establishing overt metastases in other tissues^{86,87}. However, animal studies have demonstrated that shed

tumour cells in the circulation during resection of a primary cancer enhance the development of metastases⁸⁸. This premise had been the concept behind the 'no-touch isolation technique' in which lymphovascular channels are ligated before manipulation of the tumour^{89,90}. Nevertheless, this technique has not had any significant impact on outcome in at least one controlled trial⁹¹. This discrepancy may be due to occult micrometastatic disease. Despite undergoing curative resection, over a third of patients with colorectal carcinoma will develop distant metastases or local recurrence^{92,93}. Considering this evidence, it is perhaps naive to assume that circulating micrometastases are not of clinical significance until such time as the matter is assessed comprehensively.

Clinical Implications of micrometastases

Breast carcinoma

Despite apparent curative surgery in the treatment of breast carcinoma, 25 per cent of node-negative patients still develop lymph node and distant metastatic disease. It is likely that this group of patients have occult micrometastatic disease at the time of initial surgery and that they are understaged⁹⁴⁻⁹⁷. Up to 38 per cent of patients with stage I and stage II breast cancer have demonstrable micrometastases, and their presence in bone marrow reduces relapse-free survival time⁹⁸. Meanwhile, the vascularity of the primary tumour, used as an index of angiogenesis and vascular invasion, correlates with the presence of bone marrow micrometastases⁹⁹.

The anatomical location of lymph node micrometastases is an important prognostic factor^{100,101}. If only level I nodes are involved with three or fewer foci, a favourable outcome may be expected, whereas higher nodal involvement or over three foci are associated with reduced relapse-free and overall survival rates¹⁰⁰. The intranodal location of the micrometastasis is also a prognostic determinant; micrometastases in the capsule or related lymphatics confer a better prognosis than malignant cells within the lymphoid tissue¹⁰¹.

The role of sentinel lymph node mapping in breast cancer is currently being evaluated. The sentinel lymph node concept may be validated since sentinel node biopsy with serial sectioning and immunohistochemistry appears to be an accurate method of axillary staging^{102,103}. In addition, combining sentinel node biopsy with bone marrow micrometastasis detection may enhance the staging accuracy in breast carcinoma¹⁰⁴. Serial sectioning of the node(s) improves micrometastatic detection and patients with single nodal micrometastasis identified by this method have higher recurrence rates than node-negative patients¹⁰⁵.

However, long-term results are required before widespread adoption of sentinel lymph node mapping may be recommended as an alternative to formal axillary lymphadenectomy. The overwhelming evidence suggests that the presence of nodal and/or bone marrow micrometastases is associated with a worse prognosis, but greater standardization is needed before their full impact as a prognostic indicator becomes apparent.

Colorectal carcinoma

The detection of regional lymph node metastases in colorectal carcinoma is an important prognostic indicator of and criterion for adjuvant therapy. The ability to assess accurately the extent of nodal involvement requires that the detection of micrometastasis is possible. Micrometastases may be identified using immunohistochemical methods alone or combined with radioimmunoguided localization of potential tumour-bearing tissue^{67,106}. The combined method offers the potential for finding ectopic drainage sites, but in practice the technique has a high false-positive rate^{67,106}.

Bone marrow micrometastases do correlate with outcome in colorectal carcinoma^{73,82,107}. This was shown initially using anticytokeratin antibodies but now an array of tumour-selective antibodies is available^{83,107}. More recently, the presence of cytokeratin-positive bone marrow micrometastases detected by RT-PCR was found to correlate with the stage of colorectal carcinoma⁸². Similarly, patients with colorectal cancer who have bone marrow micrometastases identified by flow cytometry are more likely to develop overt systemic metastases⁷³. However, there is no evidence at this stage that these patients benefit from adjuvant therapy.

Malignant melanoma

The main prognostic indicator in melanoma is the Breslow thickness of the primary tumour^{108,109}. Intermediate stage disease presents a dilemma as to whether elective lymph node dissection should be undertaken owing to its associated morbidity¹¹⁰. Sentinel lymph node biopsy may provide the solution to this problem, allowing node dissection to be avoided^{7,45,111}. Furthermore, sentinel lymph node mapping is useful in identifying those patients with stage II disease who have nodal micrometastases and will therefore benefit from therapeutic lymph node dissection. Morton *et al.*⁴⁵ demonstrated that patients with a positive sentinel node in early melanoma are likely to have more extensive nodal involvement. Patients with a negative sentinel lymph node biopsy have a low incidence of nodal recurrence and lymph node dissection may be avoided^{7,111}.

In one study, most patients with nodal recurrence after a negative sentinel node biopsy had micrometastases in the original specimen that were undetected because of technical constraints¹¹¹. This highlights the need for accurate detection of micrometastases in the sentinel lymph node biopsy. RT-PCR tyrosinase amplification permits very accurate identification of micrometastases and improves staging of the sentinel node⁷. Melanoma cells have been detected in the peripheral blood of patients using molecular techniques but the clinical significance is unclear¹¹². Curiously, there have been no published studies to date on the presence of bone marrow micrometastases.

Foregut cancer

The detection of early gastric cancer is increasing and the main prognostic indicator of outcome after attempted curative resection is lymph node status^{48,50,113}. A significant number of node-negative patients develop recurrence and this may be due to occult micrometastases. Approximately one-quarter of patients assigned node-negative status by traditional microscopic examination of limited sections have occult nodal micrometastasis¹¹³. Serial sectioning of the lymph nodes increases the detection of nodal metastasis and micrometastases^{48,50}. Immunohistochemistry with antibodies against CK8 and CK18 upstaged approximately one-quarter of patients with early gastric cancer undergoing curative resection in one study⁵⁰. The cytokeratin-positive group had a significantly shorter survival time than patients whose nodes were negative⁵⁰.

Bone marrow micrometastases are evident in many patients with foregut tumours^{4,72,114–116}. Over 80 per cent of rib segments resected from patients with oesophagogastric carcinoma at thoracotomy are positive for micrometastases¹¹⁴. The method and/or site of bone marrow harvest is important, as marrow aspirated from the iliac crest of these patients has a much lower micrometastatic yield¹¹⁴. A similar, but less striking, difference between micrometastatic positivity of rib *versus* iliac aspirates was recently found in breast cancer¹⁰⁴. However, micrometastases are detected in approximately one-third of marrow aspirates from patients with foregut cancer, and this correlates with the depth of invasion and degree of differentiation of the primary tumour^{4,114–117}. Therefore, the evidence suggests that the presence of nodal and bone marrow micrometastases signifies a poor prognosis in oesophagogastric cancer¹¹⁷.

Upper aerodigestive tract

Up to 60 per cent of lymph nodes removed at neck dissection for head and neck cancer are positive for

micrometastases with staining and immunohistochemical methods^{118–125}. However, many of these nodes are macroscopically positive and the number of nodes that contain micrometastases only is low (less than 15 per cent)^{119–121}. Radioguided dissection of the sentinel node(s) and associated primary lymph nodes in squamous cell carcinoma of the head and neck has been described¹²⁶. This requires attentive examination with multiple sectioning and immunohistochemical staining for accuracy. The short-term prognosis (less than 6 years) for patients with oral cancer and nodal micrometastases may be similar to that of those with or without macroscopic metastases^{123–125}. Bone marrow micrometastases are found in up to half of patients with squamous cell carcinoma of the head and neck¹²⁷. Overall, one-third of these patients had demonstrable micrometastases using antibodies to CK19. Marrow positivity correlates with stage of the tumour, clinical recurrence and disease-free survival¹²⁷. This is an evolving field in otorhinolaryngology and larger, long-term studies are required before more definitive prognostic implications become clear.

The future

There are many aspects to the micrometastasis concept that have yet to be elucidated. Are these cells a dormant representation of residual disease or do they exist in a dynamic state despite host immunity^{3,14}? What is the critical mass of cancer cells that confers prognostic implications^{70,77}? How do some patients clear their bone marrow of micrometastases after operation^{72,73}? One of the keys to these questions may be the differing location of micrometastases between cancer types, tumour location and patient groups^{72,73,76,86,87,97,104,114}. For example, is the presence of micrometastases in bone marrow of more prognostic significance than in lymph nodes or the circulation^{70,72,73,77,104,114,117,127}? In the immediate future, identification, sampling and even culture of micrometastases should permit assessment of chemotherapeutic sensitivity before the initiation of adjuvant therapy¹¹⁴. By opening a window on the cancer process, bone marrow micrometastases offer an ongoing measurement of response to systemic therapy. Neoadjuvant and postoperative cytotoxic therapies may be employed initially, but perioperative manipulations of angiogenesis and host immunity are attractive alternatives^{39–42}.

Conclusions

The identification of micrometastases has offered valuable insight into the behaviour of malignant cells. Sentinel lymph node biopsy, with serial sectioning and screening for

micrometastases, improves staging accuracy. The prognostic significance of nodal and/or bone marrow micrometastases has been established in several malignancies; the challenge now is to incorporate this knowledge into management strategies.

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Role of surgery in mild primary hyperparathyroidism in the elderly

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Background: The appropriate management of elderly patients with mild hyperparathyroidism is the subject of much debate.

Methods: A Medline literature search was conducted using the keywords 'hyperparathyroidism', 'asymptomatic' and 'elderly'. The references of the primary sources were examined for further citations. Personally collected cullings from journals and abstracts from journals were used as an additional source of data.

Results and conclusion: No prospective randomized controlled trial comparing parathyroidectomy with conservative management for patients with mild or asymptomatic hyperparathyroidism has been published. There are a number of longitudinal studies that attempt to characterize the natural history of hyperparathyroidism, but most do not stratify patients according to age when assessing outcome. None the less, it is clear that elderly patients present with a different spectrum of problems, particularly indistinct neuropsychiatric and musculoskeletal symptoms, and these are likely to be improved by surgery. The evidence allows the conclusion that the truly asymptomatic elderly patient can be successfully managed conservatively; there is a good prospect of benefit from surgery for those with symptomatic disease, and such patients should not be denied an operative option.

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Introduction

The object of this study was to analyse the data on management of primary hyperparathyroidism (HPT) in the elderly, particularly in relation to the role of surgery in the asymptomatic or minimally symptomatic patient. The first successful parathyroidectomy was performed in Vienna in 1925¹. Over the ensuing 40 years most patients with primary HPT were diagnosed only when they had bone disease or renal stones. The advent of multiphasic electrolyte analysers in the mid 1960s led to routine electrolyte screening of patients; as a result, a new clinical profile of primary HPT emerged. It now rarely presents as a serious disease and has become generally a mild condition with few, if any, symptoms (*Table 1*). Heath *et al.*² examined the incidence of primary HPT at the Mayo clinic before and after the introduction of routine serum calcium measurement. Between 1965 and 1974 the average annual incidence of primary HPT was 7.8 per 100 000 population, compared with a 3-year period after 1974 in which it rose to 23.7 per 100 000. Mundy *et al.*⁴, in a review of patients in the

Birmingham area, reported a similar incidence of 25 cases per 100 000.

The increasing numbers of patients being diagnosed with mild or asymptomatic HPT led to differing opinions about how the condition should be managed^{5–8}. A consensus conference in 1990 defined some guidelines⁹. It concluded that a diagnosis of primary HPT in an asymptomatic patient did not in all cases mandate referral for operation. However, such patients would need long-term surveillance, and should have a serum calcium concentration no more than 0.25 mmol/l above normal, have had no previous episodes of life-threatening hypercalcaemia, and have normal renal and bone status. The indications for surgery recommended by the consensus are outlined in *Table 2*. It could reasonably be argued that the weight of further evidence that has accrued since the consensus statement in 1991 renders its advice too conservative, and that there are now few patients with confirmed HPT who should be managed simply by surveillance. There remains, however, a persisting difficulty in defining who is truly asymptomatic. In assessing the literature, the terms 'asymptomatic' and 'minimally symp-

Table 1 Changes in the pattern of clinical presentation of primary hyperparathyroidism

Reference	Study interval	No. of patients	Renal disease (%)	Bone disease (%)	Gastrointestinal disease (%)	Psychiatric disease (%)	Asymptomatic (%)
Heath <i>et al.</i> ²	1965–1974	39	51	31	10	26	18
Heath <i>et al.</i> ²	1974–1976	51	4	20	8	20	51
McGeown ³	Not stated	177	72	17	4	—	3
Mundy <i>et al.</i> ⁴	1979	111	7	—	4	5	57

Table 2 Indications for surgery in asymptomatic patients with hyperparathyroidism⁹

Serum calcium concentration greater than 0.25–0.4 mmol/l above the normal range
Creatinine clearance reduced by 30 per cent compared with age-matched controls, in the absence of other causes
24-h urinary calcium concentration greater than 400 mg/dl
Bone mass more than two standard deviations below that of age-, sex- and race-matched controls
Age less than 50 years
Patients who request surgery or for whom long-term surveillance is unsuitable

omatic' cannot be taken as indicating separate populations of patients.

The peak incidence of primary HPT lies between the ages of 55 and 70 years. The Mayo Clinic study² found a peak incidence in women aged over 60 years; this group had an annual detection rate of 188.5 cases per 100 000, compared with 23.7 per 100 000 for the population as a whole. It has been claimed that 1 per cent of women over the age of 60 years will have HPT, a prevalence of 1000 per 100 000¹⁰. For men in this age group the incidence was 92.9 per 100 000. Many patients will have only a mild increase in serum calcium concentration (less than 3 mmol/l) and may not fall into the group for which surgery is indicated if they are deemed asymptomatic. The clinical problem is the sheer volume of such elderly patients with mildly raised calcium levels but who have symptoms. Such symptoms are often vague and may or may not be related to HPT, for example bone pain, lethargy, mental disturbance and constipation, all of which are common in the elderly. In the light of modern life expectancy, the mildly symptomatic patient aged 60 years may well be exposed to the metabolic effects of the disease for more than 20 years.

Natural history and mortality of primary hyperparathyroidism

The majority of studies and reviews on the management of asymptomatic primary HPT conclude that there is a need for a prospective randomized study comparing surveillance of the condition with surgery^{2,6,8,11–14}. However, such a study was set up in the UK under the auspices of the British Association of Endocrine Surgeons (BAES) and was abandoned because of low patient recruitment resulting from difficulty in persuading endocrinologists and internal medicine physicians to enter their apparently asymptomatic patients into the study while most surgeons preferred to operate on all patients referred with primary HPT¹¹. Of the published reports dealing with the long-term follow-up of asymptomatic patients, there is variability in indications for surgery and often inadequate follow-up data, making firm conclusions difficult to draw.

A prospective randomized study of 53 'asymptomatic' patients was reported by Talpos *et al.* at a meeting of the American Association of Endocrine Surgeons (AAES) and BAES in Lille, France, in May 2000 (unpublished results), but follow-up of these patients averaged only 24 months. Nevertheless, scores on the Short Form (SF)-36 health assessment test showed better results in the operated group, although these were subjective assessments and a placebo effect of treatment could not be excluded. Rohl *et al.*¹⁵ observed 30 patients with primary HPT who did not undergo operation because of their old age or lack of symptoms, along with 15 patients who had had unsuccessful neck exploration and remained hypercalcaemic. During the 3-year period of observation, no deterioration occurred in the clinical or biochemical status of these patients, and the authors concluded that non-symptomatic HPT can be managed successfully by clinical observation rather than immediate parathyroidectomy. Follow-up investigations included serum biochemistry and plain abdominal radiography, but no evaluation of renal tubular function or bone density was carried out. Scholz and Purnell⁸ performed a prospective study in which a group of 142 patients with mild asymptomatic primary HPT was followed over a period of

10 years. Follow-up included serum and urine biochemistry at intervals of 3 months, radiography of the kidneys, ureters and bladder at 6-month intervals, and annual medical examination, radiography of the thorax and hands, and intravenous urography. Thirty-three of the 142 patients eventually underwent neck exploration, 12 for renal complications, eight for a rising serum calcium concentration, four for bone disease, and the remaining nine for a variety of other reasons (four unknown). In the unoperated group 32 patients died; the cause of death was known in 27 cases. Although the authors state that death was unrelated to known complications of primary HPT, ten patients died from cardiovascular causes and four from cerebrovascular accidents, events that, given the known association of HPT with cardiovascular disease, cannot be discounted. Nineteen of the follow-up group were omitted because of lack of data, leaving 42 patients. Cumulative data for 30 of these patients revealed no objective evidence of progression of the disease, and in the remaining 12, although they presented initially with mild hypercalcaemia, a persistently raised serum calcium level could not be demonstrated. The authors concluded that, although only 33 (23 per cent) of the original group required surgery, it was not possible to predict which patients these would be. On the strength of these findings they advised that elderly patients, those with medical conditions imposing an increased surgical risk and those who refused surgery could be followed for a prolonged period with minimal risk. However, it was also noted that many patients would not submit to a long-term follow-up that was time consuming and expensive. Unfortunately, neither of the above studies^{8,15} stratified patients according to age when examining outcomes, despite advising that elderly minimally symptomatic patients could be adequately managed conservatively.

Parfitt *et al.*⁶ studied 174 asymptomatic patients over a period of 10 years who did not fit the criteria for surgery. Of this group, 68 patients were excluded because of inadequate follow-up data and the remainder were followed for a mean of 4 years. Clinical, biochemical and bone density assessments were carried out on entry to the study and repeated after at least 1 year. The authors reported no change in symptoms, no hypercalcaemic crises, no episodes of nephrolithiasis and no non-traumatic fractures. Biochemical measurements included estimation of the levels of plasma calcium corrected for albumin, total alkaline phosphatase, immunoreactive parathyroid hormone, nephrogenous cyclic adenosine 5'-monophosphate, 24-h calcium and creatinine clearance. No difference was found between initial and final mean values for any of these measurements. At the time of diagnosis, mean values for both proximal and distal forearm bone density were significantly reduced, but there was no acceleration of bone

loss during the study period, although 4 years must be considered a short mean follow-up interval.

Most of the larger longitudinal studies of asymptomatic primary HPT are available as a result of Swedish health screening programmes and the accurate recording of patients' illness and deaths by the Swedish National Board of Health and Welfare. Palmer *et al.*¹⁶ reported a population-based cohort study with 14 years' follow-up. As a result of health screening programmes in 1969 and 1971, 172 individuals with mild hypercalcaemia (mean calcium concentration 2.7 mmol/l; mean age 59.4 years) thought to be due to primary HPT were identified. These were age- and sex-matched to a group of normocalcaemic individuals from the same screening programme. The effects of hypercalcaemia were studied separately in those under and over the age of 70 years. During the 14-year follow-up, 56 (33 per cent) of the 172 hypercalcaemic persons died, compared with 78 (23 per cent) of the 344 controls ($P=0.014$); the difference in mortality rate was more pronounced in the group of patients aged 70 years or less ($P=0.0025$) than at all ages, and no difference was found at ages over 70 years. The higher mortality rate was attributed to increased deaths from cardiovascular disease. There was little deterioration in renal function in individuals in which it was initially normal. In an update of this study, following a review of the group in 1983, 17 individuals (10 per cent) had undergone neck exploration. When serum calcium was rechecked in a further 45 subjects, it was found to be less than 2.6 mmol/l¹⁷.

In a more recent study Hedback and Oden¹⁸, using the national patient registry, identified all patients diagnosed as having primary HPT during the years 1987–1994 who had undergone surgery. The number of deaths in the patient series was compared with the number of expected deaths estimated from published reports by the Swedish Central Bureau of Statistics with a mean follow-up of 3.5 years. The study group included 915 men (mean age 61.3 years) and 3546 women (mean age 64.7 years) and the control group was effectively the Swedish population matched for age, sex and calendar year. It was noted that the age at operation increased over the study period. The authors reported a significantly increased risk of death in patients with primary HPT who had been operated on compared with the risk of death in the general population ($P=0.0099$ for men, $P<0.001$ for women). Previous studies have shown malignant diseases to be associated with primary HPT, but these findings were not confirmed in this study^{19,20}. The obvious cause of the increased risk of death was cardiovascular disease, with 306.0 observed deaths compared with 168.4 expected deaths.

In an earlier study, both parathyroid adenoma weight²¹ and preoperative serum calcium levels²² were shown to be

related to the risk of death. The authors concluded that if hyperparathyroid patients were operated on at an earlier stage, before adenoma weight or serum calcium levels had reached high levels, the increased risk would not occur. They supported this conclusion with data from an earlier study²³ that demonstrated an improved survival rate for patients operated on in recent years who, they reasoned, would have had a shorter duration of disease as a result of the advent of routine biochemical screening. In this study the authors also assessed the risk of death in relation to age²³. They reported an increased risk of premature death in all age groups, although the most marked increase in relative risk of death was in the 55–70 years age group. In those over 70 years there are other competing risk factors, rendering the risk factors associated with HPT less important.

There has been one large recent study from the USA that, interestingly, was unable to demonstrate any decreased long-term survival after surgical treatment for primary HPT²⁴. Between 1980 and 1984, 1052 patients (median age 59 years) underwent surgery at the Mayo Clinic for HPT. After a median follow-up of 12 years, data were obtained retrospectively from death certificates, hospital records, the Mayo Cancer Registry, other institutions that had recently cared for the patients, and patient questionnaires. Overall survival for the study population was compared with expected survival for a matched patient population from the upper mid-west of the USA. The authors reasoned that the different outcome from the earlier Swedish studies^{16,19,23}, in which patients were operated on before the 1980s, may be explained by the Mayo Clinic's more recent series in which patients were more likely to have milder disease and to undergo operation more promptly. However, this explanation is not borne out by the most recent Swedish study¹⁸ which analysed patients operated on between 1987 and 1994. Another possible explanation for the differing results might be in the use of actuarial life insurance tables for the control group as opposed to the Swedish studies which utilized actual populations. In the Discussion of the American paper it was also noted that the patients at the Mayo Clinic were probably a medically sophisticated group, with access to good healthcare and so possible better survival²⁴.

On balance it seems that primary HPT is associated with an increased risk of death from cardiovascular causes. A few variables specific for HPT, namely parathyroid adenoma weight²¹, level of serum calcium²² and preoperative parathyroid hormone (PTH) level²⁴, have been shown to be related to the risk of death. However, the increased risk of death was not demonstrated in the population over 70 years of age in one study²⁰ and, although reported in a more recent study, the increased relative risk of death was less marked in patients aged over 70 years than in those aged

55–70 years²³. Although no randomized study is available to demonstrate that the increased risk of death is reversed by early surgical intervention, the inference from the data is that it should be. This interpretation has generated the current opinion that the fit, young patient should be operated on, even if asymptomatic.

The interventional approach to HPT is supported by another Swedish study; 48 women (aged 55–70 years), who were diagnosed as having primary HPT via population-based screening and who were previously unaware of their condition, were assessed with regard to sick leave in the 5-year period before diagnosis²⁵. Controls were 48 women from the screened population without HPT. The amount of sick leave was significantly greater in those with HPT than in controls. Long-term sick leave in the former was greater for musculoskeletal and cardiovascular diseases. The authors concluded that mild undiagnosed HPT in postmenopausal women is linked with previously unrecognized ill health and that this ill health is of importance in the clinical and economic impact of the disorder.

In summary, HPT, even mild HPT, is associated with an increased mortality rate, largely from cardiovascular disease. There is some evidence that early surgical intervention may reduce this and the levels of sick leave, although this does not appear to apply to those aged over 70 years.

Cardiovascular disease

Hellström *et al.*²⁶ showed in the 1950s that HPT is associated with hypertension, although this hypertension does not improve after operation^{27,28}. Other authors have reported an increased incidence of diabetes mellitus and disturbances in glucose metabolism^{29,30}, and higher levels of blood lipids³⁰, features acknowledged to be associated with cardiovascular disease. Hagstrom and co-workers have found that the lipid abnormalities are corrected by parathyroidectomy (Hagstrom *et al.*, unpublished findings presented to a joint meeting of AAES–BAES, London, UK, May 2000). Stefanelli *et al.*³¹ studied 54 patients with primary HPT. Echocardiography was performed before and 12 months after operation and results were compared with those of 50 age- and sex-matched controls. At baseline, 68 per cent of hyperparathyroid patients had left ventricular hypertrophy, compared with 28 per cent of control subjects. At 1 year after operation a significant regression of left ventricular hypertrophy was observed ($P < 0.001$). These authors also recorded an increased prevalence of aortic, mitral and myocardial calcification in the hyperparathyroid group, which remained unchanged after 1 year. The patients in this study were largely symptomatic with a mean serum calcium level of 3.0 mmol/l. In a similar Swedish study³², echocardiography was performed in 44 hyper-

parathyroid patients (mean serum calcium 2.8 (range 2.7–2.9) mmol/l) before and after operation; a control group consisted of 23 euthyroid patients undergoing thyroid surgery. A lower mitral valve velocity pattern was found in the hyperparathyroid group but there was no significant difference in the thickness of the interventricular septum or any significant ectopic calcifications, nor were there any significant changes after 1 year. A more recent, unpublished, study by Nilsson *et al.* (presented to the AAES–BAES meeting in London, May 2000) noted improved exercise and echocardiographic variables after parathyroidectomy, but the mean serum calcium level in their patients was higher (3.0 mmol/l).

In summary, HPT is associated with cardiovascular disease, especially hypertension, and with an increased mortality rate from cardiovascular disease. However, studies disagree about whether improvement in hypertension or left ventricular hypertrophy is predictably achieved by surgery.

Bone disease

In severe HPT, bone resorption and formation are greatly increased. Focal subcortical erosions and cystic lesions develop as a result of increased osteoclast activity and often act as sites for fracture. As seen in *Table 1*, patients nowadays rarely present with overt bone disease and skeletal survey radiographs are likely to be normal. Nevertheless, when asymptomatic patients are evaluated with bone densitometry and bone biopsy, selective reduction of cortical bone and preservation of cancellous bone can be seen^{33–36}; patients with HPT are more likely than normal controls to have experienced a bone fracture in the 5-year period before operation.

Bilezikian *et al.*³⁵ performed iliac crest biopsies and measured bone mineral density at the radius, spine and hip in patients with asymptomatic HPT, and demonstrated that cortical bone (radius) is affected more often than cancellous bone (vertebrae). Rao *et al.*³⁶ followed 80 patients with asymptomatic HPT without any interventional therapy for a mean of 40 months. At the time of diagnosis, mean values for both proximal and distal forearm bone density were significantly reduced, but during the study there was no decline in bone density other than that expected for age. Studies by McIntosh *et al.*³⁷ and by Garton *et al.*³⁸ have demonstrated that the severity of these bone changes is related to the PTH level. Longitudinal studies of bone mineral content have demonstrated a demineralization at the time of diagnosis that is partially reversed after operation; this improvement does not appear to be sustained over time^{39,40}. Elvius *et al.*³⁴ measured the bone mineral content of the distal forearm in 46 asymptomatic

women with primary HPT, 26 of whom underwent operation. The results were compared with those for 46 normocalcaemic women at entry in to the study and at 17 years' follow-up. As previously noted, the bone mineral content of the distal forearm was lower in hyperparathyroid patients than in controls. During the first 3 years after operation bone mass increased significantly in the operated group and remained unchanged in the unoperated group. However, after 17 years there was no difference in bone mineral content between the operated, unoperated and control subjects, as age-related changes supervened. It has not been demonstrated unequivocally in patients with asymptomatic primary HPT that a decrease in bone mineral content is associated with an increased fracture rate. The data are varied, with some studies reporting an increase in fracture incidence with primary HPT^{41,42}, while others demonstrate no significant difference between number of fractures expected and number observed⁴³. The potentially confounding effects of hormone replacement therapy in women have not been addressed scientifically in these patients.

In summary, HPT measurably affects bone mineral content. Although this may be altered by surgical correction of the HPT, studies disagree about the extent of clinical benefit.

Neuropsychiatric symptoms

Fatigue, anxiety, lassitude, failing memory and concentration difficulties have all been reported in HPT. These vague symptoms are often missed unless actively sought. They are also symptoms that are common in the elderly and may be misinterpreted as part of the ageing process, making it difficult to determine whether elderly patients with hypercalcaemia are indeed symptomatic.

Joborn *et al.*⁴⁴ compared self-related psychiatric symptoms in three groups of patients using the Hopkins Symptom Checklist 56-item version (HSCL). The three groups consisted of: (1) patients referred for surgery because of primary HPT ($n=30$, age 25–78 years, mean serum calcium level 2.9 mmol/l); (2) people detected in a health survey to have mild hypercalcaemia and probable HPT who had apparently been asymptomatic over a period of 15 years ($n=38$, age 48–80 years, mean serum calcium level 2.7 mmol/l); and (3) control matched normocalcaemic subjects ($n=38$, mean serum calcium level 2.4 mmol/l). The psychiatric scores were highest in the patients who had been referred for surgery (89.1) and were statistically significantly higher than those of the control group (73.8) ($P<0.001$); the unreferral hypercalcaemic cases of the health survey had only slightly higher scores (76.6) than the control group. However, when certain symptoms were

examined individually, such as crying easily, concentration difficulties, disinterest and daytime sleepiness, there was a significant difference ($P < 0.05$) between the asymptomatic health survey group and controls. The first group of patients also had the highest separate scores for these symptoms. When the three groups were analysed together, a significant correlation was found between the serum calcium level and the HSCL score ($P < 0.001$). Follow-up 1 year after operation in the first group demonstrated a clear improvement in mental health, with the score decreasing to 73.2 after operation (i.e. similar to that of the control group).

More recently, Solomon *et al.*⁴⁵ performed a similar, although smaller, study, comparing symptom checklist scores between a group of 18 patients with primary HPT and a group of 20 with benign thyroid disease. Assessment of psychological symptoms was made using a similar method to Joborn *et al.*⁴⁴ with the Symptom Checklist-90 revised system. Assessments were carried out before operation and at 1, 3 and 6 months after operation. Thirteen of the 18 patients in the hyperparathyroid group were regarded as asymptomatic; the remainder were found to have renal stones (three) or peptic ulcer (one), and one patient had both renal stones and a peptic ulcer. The mean age of the group was 56 years. Before operation in the hyperparathyroid group the mean scores were increased, indicating psychological distress, compared with those in the control group in which all the scores for the symptoms assessed were clustered around the norm ($P < 0.0001$). After operation the scores in the hyperparathyroid group decreased to approach the norm, with the greatest improvement in symptoms occurring by 1 month.

The most recent of such studies uses the SF-36 health status questionnaire¹³. One hundred and fifty-five patients were divided into two groups according to the degree of hypercalcaemia; questionnaires were filled out before operation and at 2 and 6 months after operation. Eighty-six patients had serum calcium levels lower than 2.7 mmol/l and 69 had serum levels ranging from 2.7 to 3.4 mmol/l. Patients in both groups showed profound functional status deficits compared with a normal reference population, and both groups were indistinguishable from one another. These deficits spanned both physical and mental function. By 6 months after operation scores had returned to normal or almost normal in most domains. The authors concluded that there is little relationship between patients' voiced complaints and objective assessment of their functional health status, and that patients with mild hypercalcaemia in which operation had been deferred because of lack of symptoms may well benefit from early surgical intervention.

It has been postulated that there may be a biochemical relationship between HPT and psychiatric symptoms. In another study, Joborn *et al.*⁴⁶ demonstrated depressed levels

of 5-hydroxyindole acetic acid (5-HIAA) and homovanillic acid (HVA) in the cerebrospinal fluid of 26 patients with HPT. These patients also had associated psychiatric symptoms. One year after operation there was an improvement in mental health, and in the ten patients in whom a postoperative lumbar puncture was performed levels of 5-HIAA and HVA were found to have increased.

Classical features of hyperparathyroid neuromuscular disease include muscle weakness, atrophy, hyperreflexia, abnormal gait and tongue fasciculations⁴⁷. Turken *et al.*⁴⁸ evaluated 42 patients with HPT (mean serum calcium level 11.1 mg/dl), specifically examining neuromuscular function. All patients were assessed by detailed neurological history and clinical examination. Twenty (48 per cent) of the 42 patients were found to have no neurological symptoms and a normal examination. Of the 22 symptomatic patients who complained of non-specific symptoms, such as muscle cramps and paraesthesia, ten had normal findings on examination. In the remainder the abnormal signs detected included loss of pain sensation and diminished vibratory sensation with absent reflexes. The authors concluded that the generalized weakness often reported in patients with mild HPT was related to mental depression or fatigability, which may impair voluntary effort, as opposed to a specific motor weakness.

A number of Swedish studies have performed more objective assessment of nerve conduction and muscle strength. Ljunghall *et al.*⁴⁹ demonstrated that unselected patients with HPT had normal nerve conduction velocity and neuromuscular transmission, as opposed to those with classical hyperparathyroid disease in which muscle atrophy and abnormal electromyograms have been demonstrated⁵⁰. Joborn *et al.*⁵¹ measured maximum isokinetic muscle strength (peak torque) of knee extension and flexion in 16 patients with HPT and in nine control patients undergoing thyroid lobectomy for non-functioning adenomas. Before operation they were unable to demonstrate any significant difference in muscle strength between the two groups, nor was there a relationship between subjective feeling of muscle weakness and the measured peak torque. Seven months after operation the hyperparathyroid patients had increased their muscle strength by 8 per cent ($P < 0.05$), although the relative increase in muscle strength was not significantly different from that of the control group. Patients with only slightly raised calcium values and without subjective muscular symptoms did not clearly benefit from surgery compared with controls. In a similar more recent study, maximal grip strength and torque as well as endurance were measured by means of a computer-based program⁵². In contrast, patients with HPT had significantly depressed muscular capacity compared with controls; after operation it increased in the hyperparathyroid group ($P < 0.008$) but was unchanged in

the control group. The authors found no correlation between the serum levels of calcium and PTH, and preoperative muscular capacity or postoperative improvement. By contrast, the most recent report of this aspect⁵³ showed, in a prospective randomized study, that handgrip strength, quadriceps endurance and general work capacity did not change after operation in either patients or controls. However, knee extension force improved in the primary HPT group after operation and this improvement correlated with an improvement in subjective fatigue. Furthermore, the authors found that the benefit was greater with increased age at the time of operation. The average age of their patients was only 57 years.

In summary, HPT, even when mild, is associated with measurable neuropsychiatric problems and reductions in muscle strength. Although not gross, these changes may be improved by surgery and the chance of improvement is not related to the preoperative level of calcium. The only study that was stratified for age found proportionately greater improvements after parathyroidectomy in older patients.

Parathyroidectomy in the elderly

Cervical exploration for primary HPT is successful in over 90 per cent of cases, with very low morbidity and mortality rates^{54–56}. HPT occurs more frequently in elderly patients, their symptoms may be difficult to distinguish from those of the general ageing process, and the chance of improving symptoms by operation is more difficult to judge. In addition, associated morbidity and increased age are often given as reasons for deferring surgery and choosing conservative management^{57,58}. A few recent studies have addressed the outcome of parathyroid surgery in this population.

At the University of California, 250 consecutive patients undergoing neck exploration for primary HPT were analysed for differences in clinical presentation and outcome of surgery⁵⁹. The patients were divided into two groups: 119 aged less than 60 years and 131 who were 60 years or older. There was no significant difference in presenting symptomatology between the two groups except for renal stones, which were commoner in the younger group, and hypertension, which was commoner in the older group. Surgical cure was obtained in 98.9 per cent; three patients had persistent hypercalcaemia (one younger, two older). After parathyroidectomy 83 per cent of the younger and 82 per cent of the older patients experienced substantial relief of preoperative symptomatology. The most frequently improved symptoms in the older group were fatigue (50.0 per cent), muscular weakness (48.6 per cent) and joint pain (40.9 per cent). Complications included one patient with transient vocal cord palsy, five with transient

hypocalcaemia (two younger, three older) and there was no operative death within 30 days.

In another study Chen *et al.*⁶⁰ compared symptoms and outcomes in 36 patients over 70 years with those in 148 younger patients. Again they found nephrolithiasis more often in the younger age group but they also demonstrated that symptoms of mental impairment, bone disease and fatigue were significantly more common in the elderly. The rates of cure (94.0 per cent), morbidity (5.5 per cent) and mortality (0 per cent) in the elderly were indistinguishable from those of their younger cohorts (98.0, 1.4 and 0 per cent respectively). The mean length of hospital stay, likewise, did not significantly differ between elderly (2.1 days) and younger (1.7 days) patients. The perceived outcomes of the elderly patients were obtained by a clinical nurse specialist in a postoperative interview. Of the 29 who responded, 17 reported great improvement in symptoms, six had moderate improvement and six reported no improvement; 81 per cent stated they would undergo operation again if needed.

Chigot *et al.*⁶¹ reported their experience of neck exploration in 78 patients aged over 75 years from 1978 to 1992. Again they found that the majority of patients had either neuropsychiatric or osteoarticular symptoms. Three patients (4 per cent) died in the perioperative period and significant morbidity was reported in a further 4 per cent; the mean length of hospital stay was 7 days. Although the mortality rate was higher than in other reported series, in the later period (1986–1992) involving 48 patients there was no death and the mean length of hospital stay was markedly reduced. Thirteen patients were lost to follow-up; of the remainder, 61 (94 per cent) reported a marked improvement in symptoms and only four (6 per cent) patients reported no improvement.

Conclusion

It is clear, as a result of routine serum biochemistry, that primary HPT is nowadays a different clinical entity from that which was originally described. The classical symptoms of renal and bone disease are rarely present, and many of the patients diagnosed are classed as asymptomatic. However, when more specific questions are asked, particularly in relation to vague symptoms such as general wellbeing, the actual incidence of truly 'asymptomatic' HPT is quite low^{56,62}. The usual reasons for advising surgery in an 'asymptomatic' or minimally symptomatic patient are to prevent complications such as nephrolithiasis, deterioration in renal function, accelerated bone loss and fracture. The literature seems to lend little specific support to any of these reasons, although a principal flaw in most studies is that follow-up data are often incomplete and the duration of

follow-up is short. It remains unclear whether the reported increase in cardiovascular mortality rate associated with primary HPT is a causal connection or merely an association. Improved cardiac function after parathyroidectomy can be demonstrated, but evidence that functional deficit is reversed by operation, particularly in patients aged over 70 years, is slight. By contrast, there are abundant data on the impairment in functional health status associated with HPT, and most studies demonstrate improvement after operation^{13,25,44,45,62}. Elderly patients with primary HPT present more often with indistinct psychiatric and musculoskeletal symptoms, and these are the symptoms most likely to be improved by operation. Morbidity and mortality rates related to neck exploration in the elderly are similar to those in younger age groups. As information accrues, the evidence of benefit from the surgical management of mild or 'asymptomatic' HPT increases; however, at present it is still insufficient to permit a recommendation for surgery in all elderly patients with genuinely asymptomatic mild primary HPT. These patients do not appear to come to any harm from a conservative approach, unless the serum calcium level rises to the point at which any superadded dehydration may precipitate dangerous pathophysiological changes. None the less it is important to take a thorough clinical history, paying particular attention to functional health status, as these are the symptoms that seem to be most effectively resolved by operation. Surgery therefore has a definite and constructive role to play in the management of the elderly patient with symptomatic or even mildly symptomatic HPT, but such patients should be warned that, although the operation is safe, the benefit is unpredictable.

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Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis

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Background: 'Idiopathic' pancreatitis may be diagnosed when gallstones are excluded by transabdominal ultrasonography and less common causes are not implicated by history or other investigations. Transabdominal ultrasonography may not, however, detect small stones responsible for acute pancreatitis. The aim of this study was to determine if endoscopic ultrasonography (EUS) is able to identify undetected gallstones in cases of 'idiopathic' pancreatitis.

Methods: Consecutive patients presenting with 'idiopathic' pancreatitis were assessed using EUS for the presence of gallstones or other potential causes of the attack. A control group was also imaged.

Results: Forty-four patients with 'idiopathic' pancreatitis were assessed. Ten had suffered earlier attacks of pancreatitis before this study. EUS revealed proven pathology in 18 patients. Unconfirmed pathology was evident in 14. No abnormality was seen in only nine patients. EUS failed in one patient and there were two possible false-positive results.

Conclusion: EUS is able to identify significant pathology in patients in whom a diagnosis of 'idiopathic' pancreatitis has been made following standard investigations. Patients with untreated gallstones are at risk of recurrent attacks. Idiopathic pancreatitis should not be diagnosed unless EUS has been performed.

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Introduction

Multiple aetiological factors are associated with the development of acute pancreatitis. In the UK, the commonest is gallstone disease. Various studies suggest that it is the smaller stones which transiently impact at the ampulla of Vater that are the cause of pancreatitis^{1,2}. Prevention of a further attack in patients with gallstone pancreatitis can involve urgent endoscopic sphincterotomy if the stone impacts, early sphincterotomy to prevent further stone obstruction and laparoscopic cholecystectomy to remove the stone reservoir^{3,4}. Patients who remain untreated have a 33–66 per cent chance of a recurrent attack, which can often occur within 6–8 weeks of the first attack^{2,5–7}.

Determination of the cause of pancreatitis necessitates taking a thorough history and examination to exclude alcohol abuse or identify features that may suggest an unusual cause. Gallstone disease is primarily investigated by ultrasonography to identify gallbladder stones, although it is not sensitive enough to detect the tiny stones implicated in the development of acute pancreatitis⁵. The gallbladder

and ducts may be poorly visualized, especially in the obese or in patients with an ileus due to acute illness.

A number of other investigations, including endoscopic retrograde cholangiopancreatography (ERCP), oral cholecystography, dimethyliminodiacetic acid cholescintigraphy, magnetic resonance cholangiography (MRC) and sphincter of Oddi manometry, may be used after a negative ultrasonogram if a high suspicion of a biliary aetiology persists⁸. Even so, up to 40 per cent of patients are diagnosed as having idiopathic pancreatitis^{5,6,9}.

Endoscopic ultrasonography (EUS) uses higher frequency ultrasound than conventional ultrasonography, and visualizes the gallbladder and biliary tree via the stomach and duodenum, so reducing problems of air artefact. It is potentially far more sensitive in visualizing small stones and has been shown to be as accurate as ERCP in the diagnosis of choledocholithiasis¹⁰.

The aim of this study was to evaluate the use of EUS in patients with a diagnosis of idiopathic pancreatitis to determine if gallstone disease had been missed with routine ultrasonography.

Patients and methods

Forty-four consecutive patients with a diagnosis of acute 'idiopathic' pancreatitis were studied. Acute pancreatitis was defined as an acute onset of upper abdominal pain associated with a serum amylase level of more than three times normal. A comprehensive history had been taken to identify patients in whom alcohol abuse was a potential cause and any aspects of the history, examination or biochemical findings suggesting a rare cause had prompted appropriate investigations. Conventional ultrasonography had been performed on all patients. The initial scan was usually performed during the acute illness. If no stones were identified or if unsatisfactory biliary scans were obtained, ultrasonography was repeated one or more times following resolution of the attack when full diet had been recommenced, often after discharge from hospital.

In patients with no features suggestive of gallstone disease, and no evidence of alcoholic or other aetiological factors, a diagnosis of idiopathic pancreatitis was made. This group of patients underwent EUS using a GFUM-20 echoendoscope (Olympus Optical, Tokyo, Japan).

EUS was performed after the acute attack of pancreatitis had resolved when normal feeding was re-established, often as an outpatient procedure in a similar way to standard endoscopy. Sedation was achieved with a short acting intravenous benzodiazepine (midazolam) with the addition of intravenous opioid analgesia (nalbuphine hydrochloride) in some cases. The patient was closely monitored during the procedure using pulse oximetry in addition to clinical observation.

The gallbladder was visualized by scanning at a frequency of 7.5 MHz via the antrum or duodenal bulb. The common bile duct was imaged from both the first and second parts of the duodenum (*Fig. 1*). The presence of stones or microlithiasis was noted, as was the presence of other pathology. Stones were identified as hyperechoic structures casting an acoustic shadow. Hyperechoic, mobile images that were too small to cast an acoustic shadow were considered to be sludge or microlithiasis, based on standard ultrasonographic criteria⁶. The presence of a thickened gallbladder wall was thought to be suggestive of biliary disease. The normal range of thickness of the gallbladder wall on EUS was considered to be 2–3 mm, and the diameter of the common bile duct 8 mm or less, based on previous studies of normal individuals by the authors. Changes in pancreatic morphology were identified using criteria established with transabdominal ultrasonography^{11–13}.

A control group of 25 patients, of similar age and sex distribution to the study group, was also assessed for the presence of pancreatic or biliary pathology. These patients, who were undergoing EUS for potential oesophageal or

gastric pathology, had no history of symptoms suggestive of pancreatic or biliary disease.

Results

Forty-four patients with 'idiopathic' pancreatitis were studied, 20 males and 24 females with an age range of 13–82 (median 53.5) years. Eight patients had undergone cholecystectomy from 6 months to 20 years previously. Ten patients had suffered one or more previous attacks of pancreatitis before the start of this study.

EUS was performed successfully in all but one patient who could not tolerate intubation. Abnormalities were identified in 34 patients, for two of whom the result was considered false positive. Stones in the gallbladder were found in two of 25 controls. Findings are shown in *Table 1*.

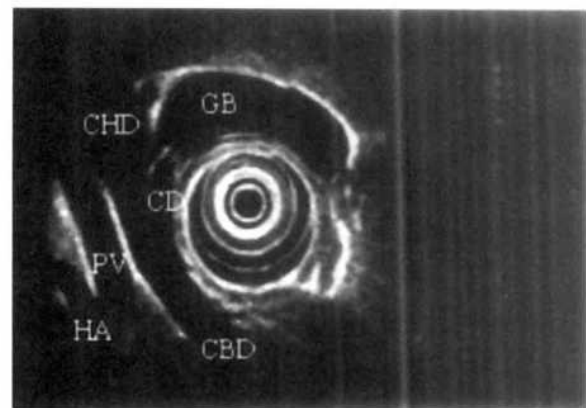


Fig. 1 Normal biliary tree and adjacent vessels on scanning through duodenal bulb. CBD, common bile duct; CD, cystic duct; CHD, common hepatic duct; GB, gallbladder; HA, hepatic artery; PV, portal vein

Table 1 Findings at endoscopic ultrasonography in 44 patients with 'idiopathic' acute pancreatitis

EUS findings	No. of patients
Gallbladder stones ± microlithiasis	9
Gallbladder and CBD stones	2
Microlithiasis ± thick-walled gallbladder	11
Stones in CBD, previous cholecystectomy	2
Stones in CBD, empty gallbladder <i>in situ</i>	2
Bulky ampulla. ?Scarred	1
Pancreas divisum	1
Pancreatic mass	1
Gallbladder polyps	1
Changes consistent with chronic pancreatitis	4
Normal	9
Failed EUS	1

EUS, endoscopic ultrasonography; CBD, common bile duct

Gallbladder stones (with or without microlithiasis) were seen in 11 patients, confirmed at subsequent cholecystectomy in nine patients, and following ERCP and endoscopic sphincterotomy in two patients in whom EUS had also identified common bile duct stones.

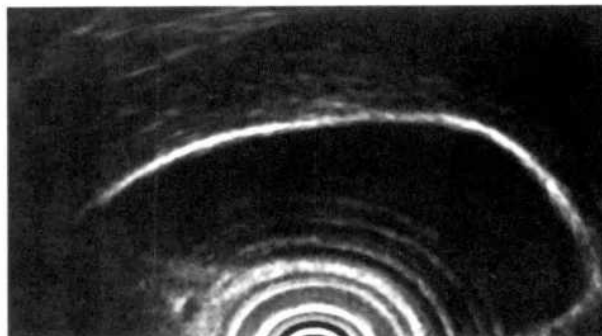
In two patients who had undergone previous cholecystectomy, stones were evident in the common bile duct and were removed at ERCP and endoscopic sphincterotomy (*Fig. 2*). Two patients were thought to have small stones in non-dilated common bile ducts with no apparent gallbladder stones. At ERCP, however, no stones were evident. It is possible that the stones had passed but this could not be proven and these cases have been considered as false positives.

Gallbladder microlithiasis without frank stones was evident in 11 patients as hyperechoic specks of calcification, too small to cast an acoustic shadow and readily distinguishable from the hypoechoic contents of the normal gallbladder (*Fig. 3a and b*). In one of these 11 patients a further attack of pancreatitis occurred 8 weeks after the first attack. On the basis of the appearances on EUS and the patient's advanced age, endoscopic sphincterotomy was performed with no subsequent attacks (follow-up 24 months). A further three patients underwent endoscopic sphincterotomy with no recurrent attacks (follow-up 10–28 months). Two patients underwent laparoscopic cholecystectomy. Histology in these cases revealed multiple 0.1-cm stones with cholesterosis of the gallbladder, in one case associated with mild chronic cholecystitis. Four patients declined treatment for microlithiasis alone (*Fig. 4*) and one patient developed unrelated illness preventing further treatment. None of these patients has developed recurrent pancreatitis (follow-up 3–18 months).

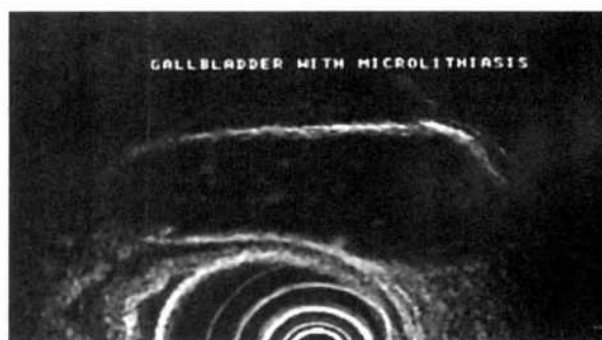
An abnormal ampulla in association with a dilated common bile duct was visualized on EUS in one patient. This appearance was presumed to be due to scarring or inflammation as there was no evidence of a mass lesion; duct

decompression was achieved with sphincterotomy, relieving symptoms over the 30 months since intervention.

In one patient an abnormal pancreatic duct was identified at EUS although misinterpreted as pancreas divisum. At ERCP an anatomically normal pancreatic ductal system was evident although the main pancreatic duct was dilated owing to papillary stenosis. Prevention of further pancreat-



a Normal



b Microlithiasis

Fig. 3 **a** Normal gallbladder and **b** gallbladder with microlithiasis containing hyperechoic specks of calcification

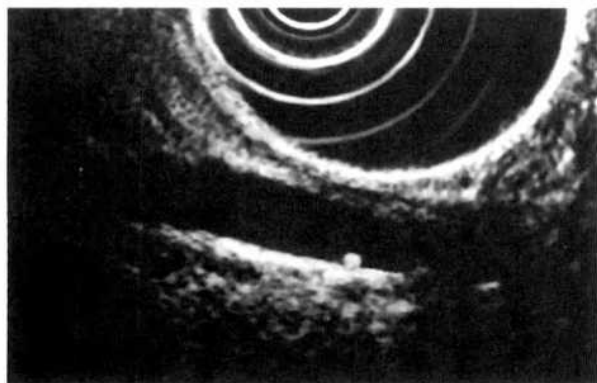


Fig. 2 Stone (2 mm) in a non-dilated common bile duct

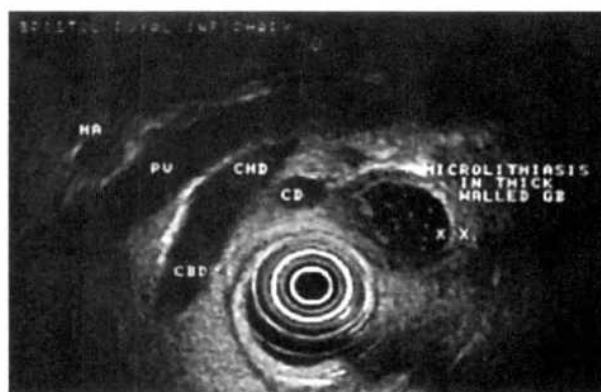


Fig. 4 Microlithiasis in a thick-walled gallbladder (GB). CBD, common bile duct; CD, cystic duct; CHD, common hepatic duct; HA, hepatic artery; PV, portal vein

itis and relief of chronic abdominal pain was obtained with a pancreatic stent (follow-up 16 months).

In four patients, ultrasonographic appearances consistent with chronic pancreatitis were noted. In one patient this was confirmed by a pancreolauryl test which demonstrated exocrine insufficiency; in another subsequent computed tomography (CT) independently identified changes of chronic pancreatitis. In the remaining two patients the presence of a heterogeneous and hyperechoic pancreas on EUS seemed consistent with early chronic pancreatitis. As ERCP was not clearly indicated and may not be able to detect early chronic pancreatitis anyway, confirmation of the correct diagnosis will rely on observation of the patients over a longer period of time than the 13–16-month follow-up currently available.

One patient had the appearance of tiny gallbladder polyps with no apparent stones and surgery for this condition as a cause of pancreatitis was not indicated. Another had a mass lesion in the lower uncinate which was hyperechoic and similar in appearance to a non-functional neuroendocrine tumour. The results of further investigations are awaited.

In nine patients the biliary tree and pancreas appeared entirely normal. One of these patients underwent laparoscopic cholecystectomy with cholangiography owing to subsequent abdominal pain as a presumed case of acalculous cholecystitis. No stones were apparent within the gallbladder or common bile duct. Histology revealed changes of chronic acalculous cholecystitis. Six patients have remained symptom free after 7–23 months of follow-up, one patient has been lost to follow-up and the other patient who experienced recurrent attacks finally admitted to a history of excessive alcohol intake. EUS failed in one patient who was unduly anxious and unable to tolerate intubation.

EUS in the control group of 25 revealed a normal biliary system in 22 patients. In two patients large solitary gallstones were visualized within the gallbladder. In one patient the pancreatic parenchyma was more hyperechoic than usual, consistent with a fatty pancreas. Microlithiasis or common bile duct stones were never seen and no other pancreatobiliary pathology was evident.

A summary of the diagnostic yield of EUS in this group of patients with acute idiopathic pancreatitis compared with the final diagnosis is shown in *Table 2*. Overall, EUS revealed proven pathology in 18 patients, of whom 13 had gallstones and two had microlithiasis confirmed at surgery. Possible pathology was evident in 14 patients but those with biliary sludge, minimal changes in pancreatic morphology and a possible mass lesion, detected only with EUS, require further follow-up to determine the significance of these findings.

There was no morbidity or death associated with EUS in this study.

Table 2 Findings at endoscopic ultrasonography compared with final diagnosis where possible

EUS findings versus final diagnosis	No. of patients
Confirmed pancreatobiliary pathology*	18
Possible pancreatobiliary pathology†	14
No pancreatobiliary pathology‡	9
False-positive diagnosis	2
Failed procedure	1

*Confirmation of stone disease at operation or of chronic pancreatitis by other independent investigations; includes a case of papillary stenosis when pathology was evident on endoscopic ultrasonography (EUS) but was misinterpreted. †Possible disease; unable to confirm pathology seen. ‡No pathology evident with no evidence of missed pathology on follow-up.

Discussion

It is recognized that further evaluation of patients with 'idiopathic' pancreatitis may disclose evidence of a potential aetiology, such as sphincter of Oddi dysfunction or unrecognized gallstone disease¹⁴.

The sensitivity of conventional ultrasonography in the detection of gallbladder stones has been analysed in several studies and ranges from 87 to 98 per cent^{5,15}. Other imaging investigations used in the assessment of suspected gallbladder stones have been shown to be clearly inferior to ultrasonography, including plain radiography, cholecystography, CT and magnetic resonance imaging^{5,16}. In addition, biochemical indicators have not reliably differentiated biliary from non-biliary causes^{5,17}.

It has long been suspected that biliary sludge may be responsible for attacks of 'idiopathic' pancreatitis^{6,9} and gallbladders removed from patients with a history of 'idiopathic' acute pancreatitis contain precipitates in over 60 per cent of cases^{6,9}. Microscopy of duodenal fluid has revealed crystals in 30–67 per cent of cases and sieving of faeces after an attack of 'idiopathic' pancreatitis revealed tiny stones of presumed biliary origin in a number of patients^{6,9}. It is difficult to be sure that the presence of biliary sludge is not a result of acute pancreatitis causing biliary stasis. Several studies, however, have shown that biliary sludge can be detected in many patients with 'idiopathic' pancreatitis but not in those with acute pancreatitis of non-biliary origin. The elimination of sludge results in fewer episodes of recurrent pancreatitis^{6,9} suggesting that sludge is a cause, and not simply a result, of acute pancreatitis. Furthermore, serial ultrasonographic investigations of patients with biliary sludge, as diagnosed by duodenal bile examination, demonstrated the transformation of sludge into unequivocal gallstones within 2 months to 4 years in untreated cases⁶.

EUS has been used in three studies to assess the gallbladder in patients with pain of suspected biliary origin in whom gallstones have not been demonstrated on conventional ultrasonography. In the first two studies a combination of EUS and stimulated biliary drainage using intraduodenal infusion of magnesium sulphate or a cholecystokinin analogue had sensitivities and positive predictive values of 90–100 per cent in the diagnosis of cholecystitis associated with gallbladder stones when transabdominal ultrasonography was negative^{18,19}. In the third study EUS was 100 per cent sensitive and 91 per cent specific in the detection of gallbladder stones in patients with a history of acute pancreatitis, with duodenal bile examination values of 50 and 82 per cent respectively¹⁷.

The possibility of undetected microlithiasis has led some groups to consider performing ERCP and endoscopic sphincterotomy in patients with recurrent idiopathic pancreatitis despite lack of proof of gallstone disease. The risks of therapeutic ERCP (including precipitating pancreatitis) are significant, however, and the long-term sequelae of endoscopic sphincterotomy are not yet known; one recent study suggested an increased risk of bile duct tumours^{20,21}. The risks of EUS are lower than those of ERCP but if gallstones are demonstrated on EUS the risks of therapeutic ERCP are more acceptable, or the patient can be offered laparoscopic cholecystectomy with or without duct exploration.

In any patient with acute pancreatitis for which no apparent cause is identified, further investigation should therefore begin with repeat transabdominal ultrasonography after the initial illness has subsided and oral intake is restored. Should this prove negative, a more sensitive way of excluding cholelithiasis is essential. This may involve MRC, endoscopic retrograde cholangiography (ERC) or EUS. However, the sensitivity of MRC and ERC in detecting the small stones or microlithiasis potentially responsible for pancreatitis is unclear. At present, therefore, EUS seems the most sensitive way of excluding a biliary aetiology. Few would dispute that the gallstones identified by EUS in 13 of the patients in this study should be treated. Scepticism persists, however, regarding the significance of microlithiasis, despite evidence from a number of sources to suggest that this may cause symptoms. As with unequivocal gallstones, which may be asymptomatic in many people, it seems likely that gallbladder sludge exists in a dynamic state in an asymptomatic population but in some is destined to develop into stones and may, as simple conglomerates of crystals, be responsible for pancreatitis and biliary pain. A prospective, randomized study would be necessary to see if treatment of microlithiasis detected by EUS in idiopathic pancreatitis resulted in fewer recurrent attacks of pancreatitis. In addition to its role in the detection of cholelithiasis,

EUS may demonstrate an alternative cause for pancreatitis and, in the age group prone to pancreatic neoplasia, is best able to provide the reassurance of excluding small pancreatic tumours^{22–24}.

Prevention of a further attack of pancreatitis by demonstrating gallstones and/or microlithiasis, through appropriate treatment, could have a significant impact on patient management and outcome. There are clear economic implications as well as healthcare gains, as severe and repeated attacks of pancreatitis result in considerable hospital expenditure.

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Biliobiliary fistula associated with gallbladder carcinoma

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Introduction

Biliobiliary fistula is a troublesome complication; it may confuse diagnostic imaging, leading to misdiagnosis, and also makes operative procedures technically difficult^{1,2}. Without a definitive preoperative diagnosis of biliobiliary fistula, surgery sometimes results in a critical biliary injury. There are few reports in the literature that describe gallbladder carcinoma with an associated biliobiliary fistula³. The clinical features of this condition remain poorly understood.

Patients and methods

From August 1979 to June 1999, 146 patients with gallbladder carcinoma underwent surgical resection; seven (5 per cent) of these patients had a biliobiliary fistula and are the subjects of this study. There were three men and four women with a mean age of 62 (range 37–78) years. The medical records and histological findings of these patients were reviewed retrospectively.

Results

Tumour location, fistula location, operative procedures and prognosis are summarized in *Fig. 1*. All patients underwent preoperative percutaneous transhepatic biliary drainage (PTBD) to relieve obstructive jaundice, prevent cholangitis and/or evaluate the biliary system^{4,5}. A preoperative diagnosis of biliobiliary fistula was made in five patients. PTBD catheter cholangiography revealed a biliobiliary fistula in only one patient (no. 5), whereas percutaneous transhepatic cholangioscopy (PTCS) showed a biliobiliary fistula in all four patients (nos 1–4) with Mirizzi syndrome. Cholangioscopic biopsy revealed no cancer invading the biliobiliary fistula where the gallstone was impacted. In the resected specimen, the tumour grew intraluminally as well as extraluminally, filling the gallbladder, and pressed a gallstone against the hepatic hilum. In three patients (nos

5–7) without Mirizzi syndrome, there was extensive tumour invasion of the hepatic hilum and the biliobiliary fistula.

Discussion

From observations, biliobiliary fistula associated with advanced gallbladder carcinoma could be classified according to the presence or absence of Mirizzi syndrome. The cause of the biliobiliary fistula in the patients with Mirizzi syndrome might have been pressure necrosis of the septum between the gallbladder and the hepatic ducts, and that in patients without Mirizzi syndrome appeared to be necrosis of the tumour.

Although PTBD catheter cholangiography revealed the fistula in only one patient, PTCS and cholangioscopic biopsy, which were performed in four patients, showed the gallstone, the biliobiliary and/or bilioenteric fistula, and no cancer invasion of the fistula and hepatic duct. These findings helped in the design of a rational resection line across the hepatic ducts. Although three patients with Mirizzi syndrome underwent major hepatic resection for marked cancer infiltration to the liver, the remaining patient had a partial hepatectomy. In two patients (nos 6 and 7), the biliobiliary fistula was detected after examination of the resected specimen. However, preoperative cholangiography demonstrated the precise extent of cancer invasion of the hepatic ducts and radical resection was performed. The presence or absence of a biliobiliary fistula did not affect surgical decision-making in the patients without Mirizzi syndrome. In patients with Mirizzi syndrome, however, it is important to determine accurately whether a biliobiliary fistula is involved by the tumour. PTCS is the best modality for this purpose.

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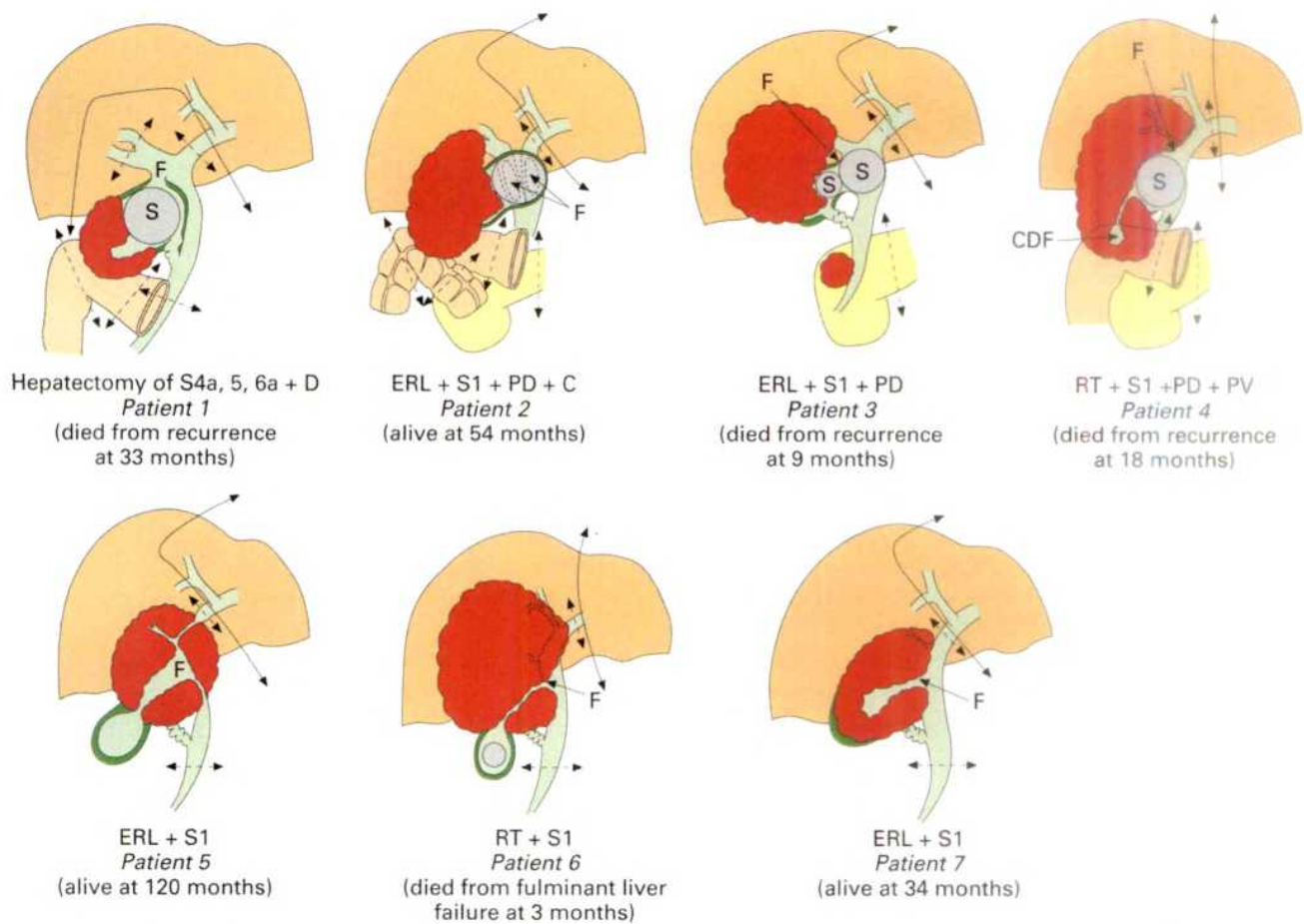


Fig. 1 Extent of the tumour and the line of surgical resection in seven patients with gallbladder carcinoma associated with biliobiliary fistula. The grey area denotes cancer, the solid line indicates the resection line of the liver, and dotted lines show the resection lines of the bile duct and adjacent organs. F, biliobiliary fistula; S, gallstone; CDF, cholecystoduodenal fistula; S4a, inferior portion of the left medial segment; S5, right anterior inferior segment; S6a, ventral portion of the right posterior inferior segment; D, partial resection of the duodenum; ERL, extended right hepatic lobectomy; S1, caudate lobectomy; PD, pancreaticoduodenectomy; C, partial resection of the colon; PV, portal vein resection and reconstruction; RT, right hepatic trisegmentectomy

Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population

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Background: Some patients with irritable bowel syndrome (IBS) may undergo unnecessary cholecystectomy. This paper describes the prevalence of cholecystectomy and IBS in a sample of British adults in Teesside. Associations between the two conditions and their relationship to consultation behaviour and socioeconomic status are described. The results are compared with those from Bristol in an attempt to determine the influence of service-related factors on the prevalence of cholecystectomy.

Methods: A postal questionnaire was sent to 4432 adults aged 20–69 years registered with six general practices. The Standard Occupational Classification was used as a proxy for socioeconomic status.

Results: In Teesside cholecystectomy was reported by 4.1 per cent of women and 1.3 per cent of men. Some 22.9 per cent of the women had IBS, and 10.5 per cent of men. Cholecystectomy was more common in patients with IBS (odds ratio 1.9 (95 per cent confidence interval 1.2–3.2); $P < 0.01$). The prevalence of cholecystectomy, of IBS and of consultation for symptoms of IBS was not influenced by socioeconomic status.

Conclusion: Symptoms of IBS may cause diagnostic confusion and unproductive surgery. Cholecystectomy may cause IBS-like symptoms, a single underlying disorder may produce symptoms in both gastrointestinal and biliary tracts, or the associations might be due to a combination of these factors.

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Introduction

The majority of patients in the general population with ultrasonographically demonstrable gallstones are asymptomatic¹. In addition postcholecystectomy studies have questioned whether the operation is always necessary² given the poor specificity of biliary symptoms³. Irritable bowel syndrome (IBS) is a condition characterized by nondescript abdominal symptoms, and patients with IBS report an excess of cholecystectomy compared with patients without IBS⁴. It is suspected that many of these operations may be unnecessary.

It is likely that cholecystectomy rates are influenced by both patient- and service-related factors, and the prevalence of cholecystectomy may reflect an interaction between these possibly synergistic variables. Factors that determine whether cholecystectomy is performed have been largely uninvestigated and, while it has been reported that healthcare-seeking behaviour may influence the illness

career of patients with IBS⁵, it is unclear to what extent such behaviour affects cholecystectomy rates.

Patient-related factors known to affect the prevalence of cholelithiasis include age, sex and ethnicity⁶. Although previous studies have investigated the association between socioeconomic variables and cholecystectomy, these studies have suffered from methodological difficulties, including low response rates⁷, samples that are not representative of the general population^{8,9} and difficulty in attributing socioeconomic status^{10–13}. Apart from addressing the impact of laparoscopic surgery on cholecystectomy rates¹⁴, service-related factors have not been investigated and it is unclear how much of an influence they exert.

In an attempt to study patient-related variables a cross-sectional study of the general population was carried out in Teesside and the relationship between cholecystectomy, socioeconomic status, IBS and consultation for IBS symptoms was examined. In addition, and in order to investigate whether service-related factors have an influence

on the prevalence of cholecystectomy, the prevalence of cholecystectomy in Teesside was compared with that reported in a study from Bristol¹.

Patients and methods

Patients were selected from the registers of six general practices that are members of the Northern Region Research Network. Before randomization the study population was stratified into 10-year age bands from 20 to 69 years of age inclusive. In two practices, consecutive numbers were assigned to each person on the registers and a one in ten sample was selected from each stratum using random number tables. In four practices a software facility on the practice computer was used to generate a similar sample. Two-thirds of the sample were from a mining and industrial area with high rates of social deprivation. The rest were from an urban area similar to the UK average for demographic and socioeconomic variables¹⁵. Ethical approval was granted by local research ethics committees. Return of a completed questionnaire was taken to imply consent to participate.

Each patient was sent a covering letter describing the study and signed by the patient's general practitioner along with the questionnaire and a reply paid envelope. Two reminders at 1-month intervals enclosed similar paperwork.

IBS was defined as abdominal pain on more than six occasions in the previous year, along with three or more of the Manning criteria¹⁶. A symptom questionnaire that had been utilized in a previous community study¹⁷ was used, and a question on cholecystectomy was added. This question was validated by giving the questionnaire to a random sample of 115 adults. Replies were received from 51 women and 49 men, and were checked against the patient's general practice records. All eight patients (six women) who reported cholecystectomy had a confirmatory hospital letter. No patient who denied surgery had a contradictory report in the notes. Data were collected regarding consultation with a general practitioner concerning any one or more IBS symptoms in the previous 2 years. Socioeconomic status was assigned to each patient using the software program 'Computer Assisted Standard Occupation Coding' in non-automatic format¹⁸. Each patient was asked their occupation and that of their partner, and was assigned to one of nine major occupational groups according to the Standard Occupational Classification (SOC)¹⁹; this hierarchical classification aggregates occupations with reference to the similarity of qualifications, training and skills. Housewives, students and unemployed patients were classified by their partner's occupation where possible. Those to whom a classification could not be

ascribed were not included at analysis when occupational classification was a variable.

Statistical analysis

Data were double entered on computer and analysed with SPSS software (version 7.5.1; SPSS, Chicago, Illinois, USA). Prevalences were derived with 95 per cent confidence intervals (c.i.). This was a cross-sectional study, so associations were analysed with the χ^2 test and odds ratios with 95 per cent c.i. Direct standardization to the 1996 UK population was performed for age- and sex-specific prevalences. The sample size was dictated by a power study performed to answer a different survey question²⁰.

Results

Of 4476 subjects selected, 38 were excluded at their general practitioner's request because of severe illness and a further six people died during the study. The postal service identified 224 people (5.0 per cent) as not resident at the recorded address. In all, 3179 questionnaires were returned, a 71.7 per cent response rate. Non-responders were more likely to be male ($P < 0.01$) and to be younger than responders. The mean age of non-responders was 38 years and that of responders was 42 years ($P < 0.001$). Compared with national UK figures²¹, responders were slightly under-representative of men and women aged 20–29 years but over-represented men and women aged 45–59 years. Ten inadequately completed questionnaires were excluded. Data from 3169 questionnaires were analysed, representing 1451 men and 1718 women.

Prevalences were calculated for the study population and by direct age and sex standardization for the 1997 UK population (standardized prevalences are shown in Table 1). The prevalence of cholecystectomy in Teesside was 2.8 (95 per cent c.i. 2.3–3.3) per cent. It was more common in women than in men (Fig. 1) (4.1 (3.2–5.0) versus 1.3 (0.7–1.9) per cent). The 12-month prevalence of IBS in Teesside was 17.2 (15.9–18.5) per cent. The prevalence for women

Table 1 Prevalence of cholecystectomy and irritable bowel syndrome standardized for age and sex to the 1997 UK population

	Cholecystectomy	IBS
Women	3.9 (3.0–4.8)	22.8 (20.8–24.8)
Men	1.2 (0.7–1.8)	10.5 (8.9–12.1)
Women and men	2.6 (2.1–3.0)	16.7 (15.4–18.0)

Values are percentages with 95 per cent confidence intervals. IBS, irritable bowel syndrome

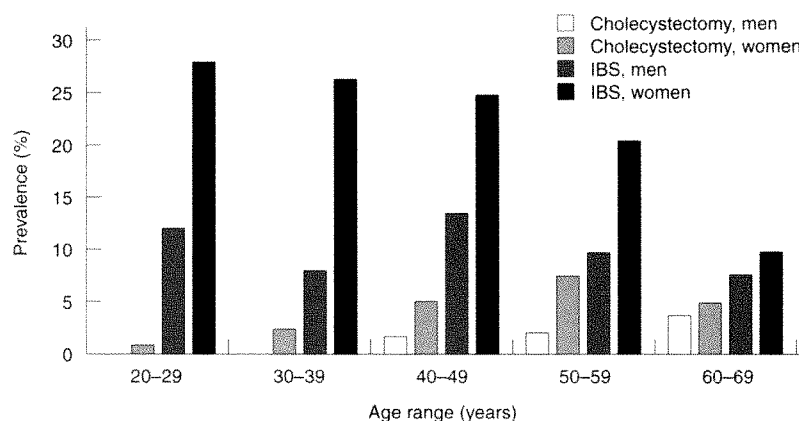


Fig. 1 Prevalence of cholecystectomy and irritable bowel syndrome (IBS) in the various age groups by sex

Table 2 Prevalence of cholecystectomy in Bristol and Teesside

Age range (years)	Bristol		Teesside	
	Women	Men	Women	Men
30-39	2.4 (2.4-2.4)	NA	3.0 (3.0-3.1)	NA
40-49	5.0 (5.0-5.0)	1.7 (1.7-1.7)	2.5 (2.5-2.5)	0.9 (0.9-0.9)
50-59	7.6 (7.6-7.6)	2.1 (2.1-2.1)	6.4 (6.3-6.4)	2.2 (2.2-2.2)
60-69	5.0 (5.0-5.1)	3.6 (3.6-3.6)	10.6 (10.5-10.7)	2.8 (2.7-2.8)

Values are percentages with 95 per cent confidence intervals. NA, not available

Table 3 Prevalence of cholecystectomy in subgroups of patients with and without irritable bowel syndrome

	Cholecystectomy in men and women (%)
No IBS	2.4 (1.7-3.1)
IBS	
Non-consulters	3.9 (3.5-4.3)
Consulters	7.5 (6.2-8.8)

Values in parentheses are 95 per cent confidence intervals. IBS, irritable bowel syndrome

and men was 22.9 (20.9-24.9) and 10.5 (8.9-12.1) per cent respectively, a female to male ratio of 2.2 : 1. The prevalence of IBS varied for each 10-year age group, being more common among women in each age group, but it showed a smaller sex difference in older age groups (Fig. 1). Patients in Teesside with IBS were more likely to have had a cholecystectomy: 4.6 *versus* 2.4 per cent in controls (odds ratio 1.9 (1.2-3.2); $P < 0.01$).

The age- and sex-specific prevalences of cholecystectomy were calculated from data reported in a similar cross-sectional survey of a Bristol population¹. The results for the two studies are reported in Table 2. As the 95 per cent c.i. for the two population prevalences do not overlap for any age group or sex, they are dissimilar at the 5 per cent level of significance.

A total of 2930 people were classified according to occupation. There was no statistically significant association between SOC and cholecystectomy ($\chi^2 = 12.04$, d.f. = 8, $P > 0.4$), or between SOC and IBS ($\chi^2 = 15.4$, d.f. = 8, $P > 0.07$).

Of 546 patients with IBS, 109 (20.0 per cent) had consulted their general practitioner regarding at least one IBS symptom in the previous 2 years. Consultation behaviour did not fully account for the association between cholecystectomy and IBS. There was a gradient in the prevalence of cholecystectomy, which was lowest in subjects without IBS, higher in those with IBS who had not consulted, and highest in those with IBS who had consulted concerning IBS during the previous 2 years (Table 3).

Among patients with IBS, consultation behaviour for IBS was not influenced by SOC ($\chi^2 = 4.51$, d.f. = 8, $P > 0.8$). Similarly the prevalence of cholecystectomy in patients with IBS was not influenced by SOC ($\chi^2 = 11.8$, d.f. = 8, $P > 0.2$).

Discussion

General practice registers in the UK offer the best means of sampling the general population²² as registration is almost complete for the UK population and address details are accurately maintained and regularly updated. The overall questionnaire response was good at 71.7 per cent, but younger age and male sex were indicators of lower response. Non-responders were not followed further as the research ethics committee had required return of the questionnaire to indicate consent to participate.

The prevalence of cholecystectomy in Teesside is different to that in Bristol for each sex and age group. The two populations are predominantly white British, although they differ in that Teesside has a significant population originating from the Asian subcontinent and Bristol has a considerable population of African Caribbean origin. Patients were not asked to identify their ethnic origin, nor were data recorded regarding body mass; it is, however, unlikely that the differences between these two populations are related to these factors. It may be that service-related factors account for the differences, and further research is required to explain these findings. To assist future comparisons, prevalences have been standardized to the UK population.

In this study a history of cholecystectomy or a report of IBS was not associated with socioeconomic status as identified by the SOC. In addition, socioeconomic status was not shown to influence consultation behaviour regarding IBS. This is a little surprising and may partly reflect reliance on occupational data to identify socioeconomic status. It may be that recording educational attainment would have been more informative as this might be more accurate in indicating how an individual would utilize healthcare services. Other studies on consultation behaviour that did not address socioeconomic variables have shown that the severity of abdominal pain and concern about the possible serious significance of abdominal symptoms are important influences on consultation behaviour^{23,24}. It might be that these factors supervene over socioeconomic factors, at least in the UK primary healthcare system where access to healthcare is universal and free at the point of contact.

While it is acknowledged that the Manning criteria will not have 100 per cent specificity for IBS, the presence of two Manning criteria has been shown satisfactorily to identify

people with IBS. Three Manning criteria were used in this study in order to increase diagnostic specificity. The Rome criteria²⁵ were not used as they were undergoing revision and validation at the time of the study, but it has been shown that Manning and Rome criteria identify largely the same population²⁶. The ascending prevalence of surgery among subsamples of the population (*Table 2*) is striking, particularly when substantial differences in psychopathology and health beliefs have been reported between patients with IBS who do and those who do not consult²⁴. Although the gradient of surgical intervention may be explained by an increased likelihood to refer people who consult with IBS symptoms for a specialist opinion, the persistence of associations between IBS and surgery, even among those who have not consulted about even one IBS symptom in the previous 2 years, seems to indicate that a tendency for increased symptom reporting is unlikely to account fully for the observed associations.

This study has identified a considerable volume of operations among patients with IBS, amounting to an excess of 16 (95 per cent c.i. 9–23) cholecystectomies per 1000 women with IBS aged 20–69 years. There are a number of possible explanations. Patients with IBS may have undergone inappropriate surgery, with IBS symptoms being misinterpreted by both the referring general practitioner and the surgeon as due to a condition for which surgery would be indicated²⁷. Alternatively patients may have developed IBS symptoms as a result of operation²⁸. A prospective study to investigate whether IBS predisposes to cholecystectomy has not been performed but would help to clarify the relationship between these conditions and identify the factors that lead to referral. It would also help to investigate the influence of the general practitioners' diagnosis on the decision to operate, as well as to identify whether the excess of cholecystectomy is accounted for mainly by an excess of emergency operations. A further possibility is that an underlying disorder capable of producing symptoms in more than one physiological system²⁹ may account for gastrointestinal and biliary symptoms in many patients³⁰.

This study has shown that the prevalence of cholecystectomy may be influenced by service- and patient-related variables. It also shows that the prevalence of cholecystectomy varies with geographical location, with the coexistence of IBS, and with consultation behaviour regarding symptoms of IBS. Future research may concentrate on the longitudinal history of cholelithiasis and IBS, with investigation of the incidence of cholelithiasis among patients with and without IBS. It would be helpful to investigate factors influencing the patient's decision to consult a general practitioner, the decision to refer to a surgeon, and the latter's decision to operate. It would also be

interesting to investigate further the influence of socio-economic factors, and in particular to examine the relationship between educational attainment and cholecystectomy.

Acknowledgements

The authors thank the patients, doctors and staff of Eaglescliffe Medical Practice, Thornaby and Ingleby Barwick Medical Group, the Skelton Group Practice, Moorland's Surgery, Sedgfield Group Practice and Tennant Street Surgery. They also thank Professor A. P. S. Hungin, H. O'Flanagan, P. Kelly and Clare Tait. T.M.K. held a Regional Research Training Fellowship during part of this study and was attached to the Department of Primary Health Care, University of Newcastle upon Tyne. This work was supported in part by grants from the Scientific Foundation Board of the Royal College of General Practitioners, the Research and Development Directorate of the Northern Regional Health Authority, the Cleveland Primary Care Research Panel and the Primary Care Society for Gastroenterology.

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A Letter of Apology

For the Sir Nicholas Attygalle Oration 1996, I submitted the results of some research work I did in 1994/1995 at the University College London surgical research laboratory, under the supervision of Mr Chu Yiu Yiu, on the subject of molecular markers in metachronous colorectal cancer, with written permission from my supervisor. This oral presentation was later submitted to the *Ceylon Medical Journal* in September 1996, at the request of a member of its Editorial Board.

My submission to the *Ceylon Medical Journal* had to be revised extensively, and it was only published in the *Ceylon Medical Journal* in December 1999¹.

During this period of writing, my supervisor (Mr Chu Yiu Yiu) and colleagues had submitted this work to the *British Journal of Surgery*, which published the article².

The results reported in the *Ceylon Medical Journal* and the *British Journal of Surgery* are substantially the same, and incorporated the work that I had collaborated in performing with my supervisor and other colleagues as stated in the first paragraph.

I apologise to the Editorial Boards of the *British Journal of Surgery* and *Ceylon Medical Journal* for my act of omission, in failing to notify the respective boards, that the results reported in the *British Journal of Surgery* article would be incorporated in to the article that I had submitted to the *Ceylon Medical Journal*.

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This letter was published verbatim in the *Ceylon Medical Journal*.

Appendicectomy and perioperative mortality in patients with liver cirrhosis

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Introduction

Case series have indicated that patients with liver cirrhosis who require surgical intervention are at increased perioperative risk, mainly as a result of bleeding and infection¹⁻³. Appendicectomy is a common operation which has a low risk of complication and mortality.

A population-based nationwide cohort study was conducted in Denmark to examine the perioperative 30-day mortality after appendicectomy in patients with liver cirrhosis.

Patients and methods

The study was conducted in Denmark (population 5.2 million) and involved patients operated on between 1 January 1977 and 31 December 1993.

The study cohort was identified in the Danish National Registry of Patients, which contains information on all hospital admissions since 1977⁴. Diagnoses and surgical procedures were classified according to the International Classification of Diseases, 8th edition (ICD-8). Patients were included if they had been discharged with a diagnosis of alcoholic cirrhosis (ICD-8, 571.09), primary biliary cirrhosis (571.90), non-specified cirrhosis (571.92), chronic

hepatitis (571.93) or 'other types of cirrhosis, alcoholism not indicated' (571.99).

Patients who had undergone appendicectomy (ICD-8, 430.00) following a diagnosis of liver cirrhosis were then identified. Those who had undergone appendicectomy associated with other operations (e.g. colectomy) were excluded.

The control group consisted of all Danes who had undergone appendicectomy in the same time period. To adjust for co-morbidity in the statistical analysis, the Charlson Co-morbidity Index was estimated for each patient⁵. Subjects with liver cirrhosis who died within 30 days were identified.

Statistical analysis

Logistic regression models were used to estimate the association between liver cirrhosis and 30-day case fatality, and adjusted for age, sex and co-morbidity.

Results

Of 22 840 patients with a diagnosis of liver cirrhosis, 69 underwent appendicectomy. The 30-day mortality rate was 9 (95 per cent confidence interval (c.i.) 3-18) per cent in cirrhotic patients, compared with 0.7 (95 per cent c.i. 0.6-0.8) per cent among the 58 982 controls (*Table 1*). Causes of deaths were: bleeding from gastro-oesophageal varices (two patients), peritonitis, pneumonia, 'cirrhosis hepatis' and ischaemic heart disease (one patient each). The risk of 30-day mortality, adjusted for age, sex and co-morbidity, and estimated as odds ratio was 8 (95 per cent c.i. 3-20).

Discussion

The study showed an increased postoperative mortality rate in patients with liver cirrhosis undergoing appendicectomy. This finding corresponds to existing studies of liver cirrhosis and other types of abdominal surgery¹⁻³. It seems that liver cirrhosis is associated with an increased mortality rate, even when minor surgical procedures are performed where the stress response may be low.

The main strengths of the present study are the large size compared with existing studies, the uniformly organized healthcare system that allowed a population-based nationwide design, and the completeness of follow-up. However, the study lacks some clinical details, such as indications for operation and the degree of liver cirrhosis.

The increased mortality rate in patients with liver cirrhosis who undergo minor abdominal surgery should be examined in other data sets before serving as basis for recommendations to surgeons.

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Table 1 Total case fatality and age-distributed death in Danish patients undergoing appendicectomy

	Liver cirrhosis cohort		Control cohort	
	Total	No. of deaths	Total	No. of deaths
Total population	69	6 (9)	58 982	413 (0.7)
Age (years)				
20-54	28	3 (11)	46 740	44 (0.1)
55-70	32	2 (6)	7 527	71 (0.9)
>70	9	1 (11)	4 715	298 (6.3)

Values in parentheses are percentages

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Need for secondary interventions after endovascular repair of abdominal aortic aneurysms. Intermediate-term follow-up results of a European collaborative registry (EUROSTAR)

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Background: The frequency of secondary interventions after endovascular repair of abdominal aortic aneurysms (AAAs) was assessed and correlated with findings at clinical and imaging examination during follow-up.

Methods: Data were studied from 1023 patients with a follow-up of 12 months or longer, collected by 56 institutions in a multicentre data registry (EUROSTAR). Surveillance data were provided by the centres between September 1996 and November 1999.

Results: Overall, 186 patients (18 per cent) had a secondary intervention occurring a mean of 14 months after the initial endograft procedure. Twelve per cent of the interventions were transabdominal, 11 per cent consisted of an extra-anatomic bypass and 76 per cent involved a transfemoral procedure. The rates of freedom from intervention at 1, 3 and 4 years were 89, 67 and 62 per cent respectively. Migration (relative risk (RR) 8.9) and rupture (RR 22.6) were the most frequent causes of secondary transabdominal interventions. Graft limb thrombosis was the principal indication for extra-anatomic bypass (RR 37.5 for clinical evidence of graft limb thrombosis). Endoleak, graft kinking, stenosis or thrombosis and device migration were significant causes for secondary transfemoral interventions (RR 2.5–6.9).

Conclusion: The high incidence of late secondary interventions is a cause for concern with regard to broad application of endovascular AAA repair, and emphasizes the need for lifelong surveillance.

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Introduction

Endovascular repair of abdominal aortic aneurysms (AAAs) has developed considerably since the technique was described by Parodi *et al.* in 1991¹, and the first early results were published^{1–7}. Now that endovascular aneurysm repair (EVAR) can be used in a significant proportion of patients with AAA, accurate assessment of its long-term efficacy is essential. Unlike conventional AAA surgery, endovascular repair carries a small, continuous risk of rupture. For this reason lifelong surveillance is required to identify those at risk. Continued or recurrent growth of the aneurysm, with or without endoleaks, and device migration are associated with an increased risk of rupture^{8,9}. An annual rupture rate of 1 per cent after EVAR has been reported⁹. The actual rate of rupture may be influenced by prophylactic secondary interventions during follow-up. In addition to endoleak and

growth or rupture of the aneurysm, kinking, stenosis or thrombosis of the limbs of the endograft are events that also require secondary interventions. This constitutes an additional burden for the patient, as well as for healthcare resources¹⁰. Thus, the need for secondary interventions is an important indicator of intermediate- and long-term success of EVAR. These late procedures can be graded according to their extent as follows: transabdominal surgery with or without preservation of the endograft, extra-anatomic bypass and transfemoral endovascular reintervention.

This report analyses patients included in a multicentre collaborative European registry (EUROSTAR). At present over 2000 patients have been enrolled in the central database. The aim was specifically to study late reinterventions in 1023 patients who had passed the first postoperative year. The number of different procedures was analysed in

detail. In addition, findings at follow-up surveillance that were associated with the need for secondary intervention were evaluated.

Patients and methods

Patients and organization of registry

The EUROSTAR registry was established in 1996 for the purpose of collation and analysis of data from patients having endovascular treatment for AAA. The initiative for this project came from an international group of vascular surgeons and interventional radiologists. A study protocol and case record forms (CRFs) were designed by a steering committee¹¹. The secretariat of the EUROSTAR organization is located at the Royal Liverpool and University Hospital in the UK, and the Data Registry Center at the Catharina Hospital in Eindhoven, The Netherlands. The inclusion criteria, as defined in the registry's protocol, comprised elective treatment for AAA and vascular anatomy suitable for the implantation of a stented tube or a bifurcated prosthesis. A detailed account of the organization of the EUROSTAR registry, and a report on early complications after EVAR, has been published previously^{11,12}.

Baseline data on suitable patients were recorded in a standardized fashion by the participating institutions and submitted for inclusion to the EUROSTAR Data Registry Center. Findings at follow-up visits, which involved clinical examination and computed tomography (CT), were recorded on data forms and returned at regular intervals to the Data Registry Center for processing and analysis. A total of 2176 patients operated on between January 1994 and November 1999 survived the first postoperative month. Of this group 1023 patients had follow-up for 12 months or longer. This patient cohort, which was treated in 56 institutions, constituted the basis of the present study. Secondary interventions performed at the time of the initial procedure were not taken into account. Excluded from this analysis were 1153 patients: those without a secondary intervention with a follow-up of less than 1 year ($n = 1004$), those who had died within the first year ($n = 114$) and patients who had undergone a primary conversion in the first month ($n = 35$). In the study cohort 281 patients had EVAR before September 1996, the date the registry commenced. Data for these patients were collected retrospectively on CRFs and entered on to the database. For the remainder of the patients prospective enrolment was mandatory; there was pretreatment registration and analysis was made according to the intention-to-treat principle.

There was a strong male predominance in the series (90 per cent). The mean age of the patients was 69 (range 42–

Table 1 Baseline characteristics in 1023 patients with follow-up of more than 12 months after endovascular aneurysm repair

	No. of patients
Male sex	925 (90)
ASA physical status classification	
I	88 (9)
II	400 (39)
III	437 (43)
IV	61 (6)
Not defined	37 (4)
Device type	
Vanguard	521 (51)
Stentor	243 (24)
AneuRx	125 (12)
Talent	78 (8)
Ancure	28 (3)
Zenith	10 (1)
Other	18 (2)

Values in parentheses are percentages. ASA, American Society of Anesthesiologists. Device manufacturers are as follows: Vanguard, Boston Scientific, Natick, MA, USA; Stentor, Mintec, Freeport, Bahamas; AneuRx, Medtronic, Santa Rosa, CA, USA; Talent, World Medical, Sunrise, FL, USA; Ancure, Guidant, Menlo Park, CA, USA; Zenith, Cook, Karlslunde, Denmark

90) years. The median size of the aneurysm was 56 (range 28–150) mm. Six per cent of the patients were classified as American Society of Anesthesiologists (ASA) grade IV; the remainder were in ASA grades I, II or III (*Table 1*). Ninety-two per cent of the patients received a bifurcated device, 6 per cent an aorto-aortic straight tube endograft and 2 per cent an aortouni-iliac device combined with a femoro-femoral bypass. Fifty-one per cent of the patients were treated with a Vanguard device (Boston Scientific, Natick, MA, USA). The other patients were treated using a variety of other commercial devices (*Table 1*).

CT with contrast enhancement of the abdominal blood vessels was the most frequently used method of imaging at follow-up visits. However, contrast angiography, magnetic resonance angiography and duplex imaging were also used at the discretion of the responsible physicians as follows: CT (in 68 per cent of all visits), angiography (13 per cent), magnetic resonance angiography (2 per cent) and duplex imaging (17 per cent). For this analysis, data from one examination (the highest in ranking order) per visit were included. Plain abdominal radiographic studies were not included in the analysis, as this examination was performed in only a small proportion of patients.

Outcome events and associated variables

All secondary interventions occurring after the first month of follow-up were included in the analysis. Complications

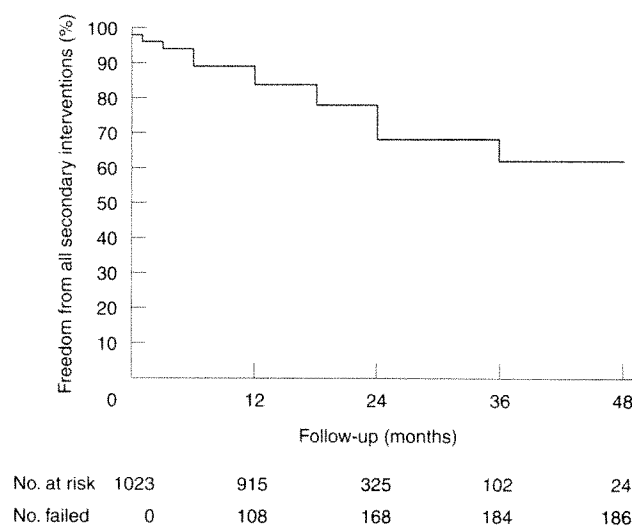
Table 2 Secondary interventions and findings at follow-up surveillance

Secondary interventions	Surveillance variables correlated
Transabdominal secondary intervention	Endoleak proximal
With conversion to open procedure	Endoleak midgraft
With preservation of endograft function	Endoleak distal
Extra-anatomic secondary intervention	Reinjection from side branch
Transfemoral secondary intervention	Kinking of endograft
	Stenosis/thrombosis of device (limb)
	Migration of device

and reinterventions before discharge from the hospital were not considered. Interventions were graded according to their magnitude into the following categories: (1) procedures requiring laparotomy, either with conversion to open aneurysm repair or with preservation of endograft function; (2) extra-anatomic procedures not requiring a laparotomy; and (3) secondary transfemoral interventions, either by the percutaneous route or via an exposed common femoral artery. In patients who underwent multiple procedures only the most extensive procedure was taken into account. Cumulative rates of freedom from intervention were assessed by life-table analysis in each category. Details of the indications for secondary interventions were analysed and correlated with each category of intervention. Indications consisted of the clinical events, aneurysm rupture and graft limb occlusion, and findings on surveillance imaging (Table 2). Differences in clinical and imaging findings between subgroups with and without specific secondary interventions were assessed by χ^2 tests, and $P < 0.05$ was considered to represent a significant difference. Relative risk (RR) values were presented if subgroup differences were statistically significant.

Results

The mean follow-up for the whole study population of 1023 patients was 20 months. Overall 186 patients (18 per cent) had a secondary intervention, occurring at a mean of 14 months after the initial endograft procedure. The mean (s.d.) number of initial procedures per centre was 18(30) (range 1–188) and the mean percentage of secondary interventions 15(18) (range 0–100). There was no significant difference in the rates of reintervention, adjusted for duration of follow-up, between the different device labels, bifurcated and other graft configurations, or modular and unipiece endografts. The total follow-up in patients with a secondary procedure (including the period after the intervention) was 25 months. Twenty-three (12 per cent) of the interventions were via a transabdominal approach, 21 (11 per cent) by extra-anatomic bypass and 142 (76 per cent) involved a transfemoral procedure. Secondary

**Fig. 1** Freedom from all secondary interventions

interventions were required at a continuous rate throughout the 4-year follow-up interval. The rate of freedom from intervention at 1, 3 and 4 years was 89, 67 and 62 per cent respectively (Fig. 1).

Transabdominal secondary intervention

Of the 23 transabdominal interventions, 20 included conversion to open repair with a sutured graft, while in three the initial endovascular repair was preserved. During these latter procedures an occluded iliac device limb was replaced by a conventional prosthesis in two patients, and an endoleak repaired in one patient. The indications for late conversion to open surgical aortic repair were rupture of the aneurysm in four, migration of the device in six, endoleak in five and complete occlusion of the graft in one. More than one indication was present in two patients. Details about the indication for secondary intervention were unavailable for two patients.

Transabdominal interventions occurred at a low rate throughout the 4 years of follow-up. The cumulative rate of

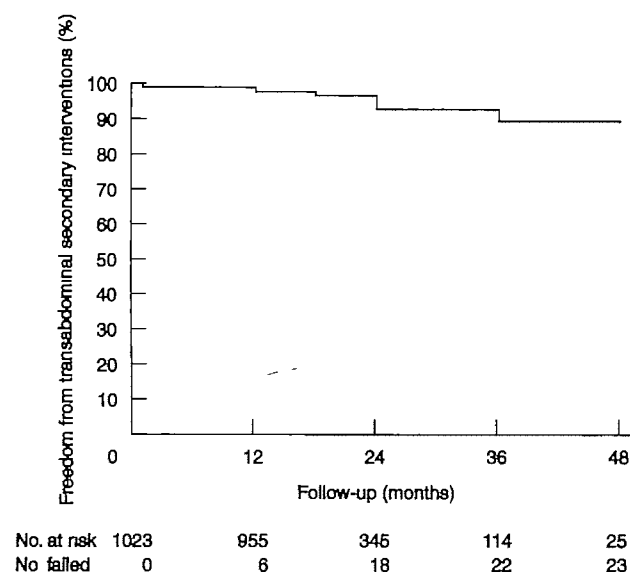


Fig. 2 Freedom from transabdominal secondary interventions

freedom from transabdominal secondary intervention was 99 per cent at 1 year, 93 per cent at 3 years and 90 per cent at 4 years (*Fig. 2*). Of the findings on surveillance imaging, proximal and midgraft endoleak correlated significantly with transabdominal intervention (RR 12.6 and 4.5 respectively), as did migration (RR 8.9). Rupture of the aneurysm was the principal clinical indication for transabdominal secondary intervention, with an RR of 22.6.

Extra-anatomic secondary intervention

All 21 extra-anatomic interventions consisted of a femoro-femoral bypass. In two instances an additional surgical procedure for peripheral revascularization was undertaken and in another two patients an additional endovascular intervention was performed; in one a stent was used to treat an iliac artery stenosis and in the second patient an extension endograft was applied. The primary indication for extra-anatomic bypass was graft thrombosis in 14, stenosis in three and kinking in four patients. The cumulative rate of freedom from extra-anatomic secondary intervention was 98 and 97 per cent at 1 and 3 years respectively (*Fig. 3*). The only variable observed on surveillance imaging that correlated significantly with this event was thrombosis or stenosis of a limb of the graft (RR 5.6 for imaging studies and 37.5 for clinical assessment).

Transfemoral secondary intervention

Details of the procedure were available in 61 of 142 late transfemoral interventions. There were six percutaneous

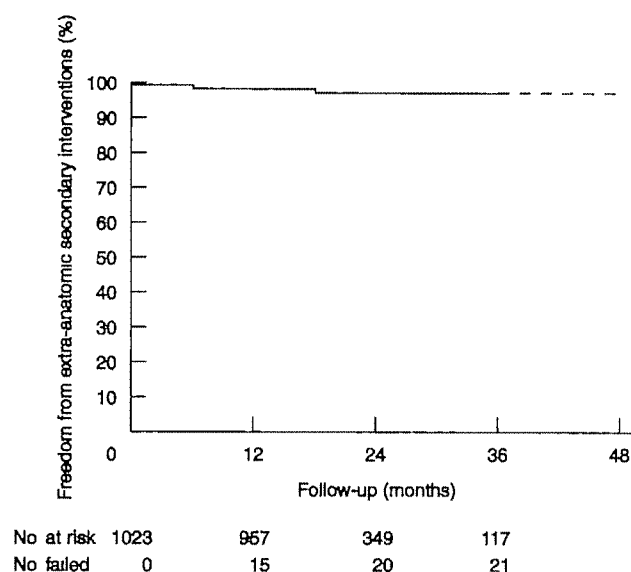
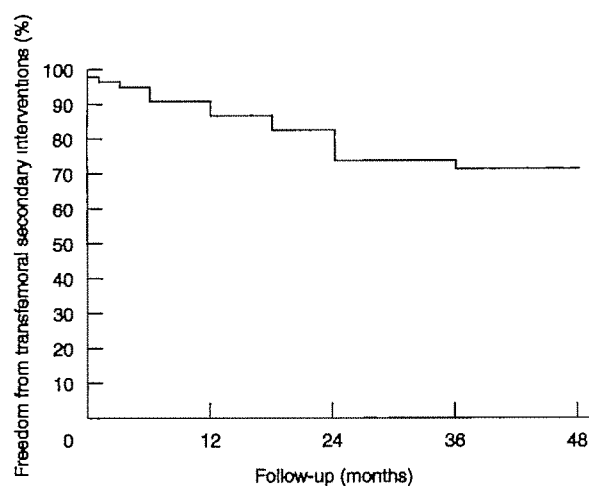


Fig. 3 Freedom from extra-anatomic secondary interventions. Broken line denotes standard error greater than 10 per cent

angioplasties, four stent implantations and ten embolizations of inferior mesenteric or lumbar arteries. Covered stents or endografts were used for bridging, covering or extending the iliac limbs of a previously implanted endograft in 29 patients. Aortic devices were extended by a proximal cuff in five and a distal cuff in three patients. Implantation of a new bifurcated device was the procedure in four patients. The rate of freedom from transfemoral secondary intervention was 91, 75 and 72 per cent of the study population at 1, 3 and 4 years respectively (*Fig. 4*). All of the imaging variables that were assessed correlated significantly with this type of intervention, i.e. endoleak at any site, kinking, stenosis or thrombosis, and device migration (RR 2.5–6.9). Of the clinical events, graft limb thrombosis was also associated significantly with transfemoral reoperation (RR 2.6).

Late death in study groups

The 3-year cumulative survival rate of patients without a secondary intervention was 90 per cent (41 late deaths), while in those who had a secondary intervention it was 85 per cent (13 late deaths). This difference just reached the level of significance ($P=0.05$). Late death was more frequently observed in the group of patients with transabdominal reintervention (13 per cent; three of 23) than in patients with transfemoral or extra-anatomic interventions (6 per cent; ten of 163). However, in none of the three individual reintervention groups did late survival differ



No at risk	1023	923	332	107	25
No failed	0	87	130	141	142

Fig. 4 Freedom from transfemoral secondary interventions

statistically from that in the group without reintervention. The causes of death in patients with secondary intervention were related to the stent-graft treatment or the aortic aneurysm in four patients, unrelated in eight and unknown in one. Of patients who did not have secondary interventions, three died from causes related to the AAA, 34 died from unrelated causes and in four the cause was unknown. AAA-related deaths consisted of rupture in five patients (two had transabdominal, one had extra-anatomic and one had transfemoral procedures; one had no reintervention) and infected endograft in two patients (without secondary interventions). Non-related deaths were from cardiac causes (15), stroke (4), malignancy (12) or other causes (11).

Discussion

Following the introduction of EVAR, application of this technique has developed rapidly. However, reliable information about its efficacy has been slow to emerge. The early published series consisted of small numbers of patients, and many of the recent publications involve a relatively limited follow-up, often less than 1 year^{13,14}. In a previous EUROSTAR report an account was given of the first month's complications and reinterventions¹². To study late adverse events, and the incidence of secondary interventional treatment, the authors chose to study a group of patients included in the registry that had at least 1 year of follow-up. The mean follow-up in this subgroup was 20 months, and a sufficient number of patients was included to allow meaningful conclusions. The overall rate of intervention was worrying; the cumulative rate of freedom

from intervention at 4 years was 62 per cent, which equates to an intervention rate of almost 10 per cent per year. Considerable differences in incidence existed between different categories of reintervention.

Of late transabdominal procedures, 20 of 23 consisted of conversion to open AAA repair. Cuypers *et al.*¹⁵, in an analysis of the risk of conversion, observed that primary and first-month conversions were most often related to problems of access and migration of the device. In contrast, the most common causes of late conversion were persisting endoleak or rupture. In the present series of patients with longer follow-up, endoleak and/or migration was the prime indication in half of all transabdominal secondary procedures. Rupture was the reason for conversion in only four of the patients who had transabdominal intervention. With regard to other reasons for conversion, device failure in different forms has received considerable attention recently. Breakage of the polypropylene sutures that connect rows of nitinol stents in Vanguard devices has been reported. Although this was usually an independent finding, not associated with any clinically relevant events, this was not always the case. In one patient included in the present series, and recently described by Breek *et al.*¹⁶, fabric holes caused by permanent friction damage by the protruding extremity of a metal stent zig were identified. This resulted in secondary pressurization and rupture of the aneurysm sac.

Type I or attachment site endoleaks were the most frequent indication for abdominal secondary procedures. Distal limb dislocation may be due either to inadequate overlap with the iliac artery at the primary procedure or later anatomical distortion of the device¹⁷. Proximal migration or endoleak may be due to undersizing or inadequate fixation of the stent-graft^{18,19}. Alternatively, late dilatation of the infrarenal neck may occur with similar effects^{20,21}. While the incidence of secondary proximal migration or endoleak was low in the present EUROSTAR cohort, there was significant correlation between this event and secondary abdominal intervention. Some suspicion may be justified that this late complication will be observed more frequently in the future as follow-up increases. A third mechanism of attachment site endoleak is the recurrence of an endoleak that had sealed spontaneously by thrombosis²². Thrombosed endoleaks are not identifiable on CT or angiography, but may be associated with increased intrasac pressure or 'endotension'²³. In this situation, growth of the aneurysm may be the sole reason for conversion to open surgery. Rupture of an aneurysm has been described without a visible endoleak²⁴. Rupture associated with late disconnection of the iliac limb from the aortic device²⁵ occurred in at least one patient in this EUROSTAR series. Aneurysm rupture after endograft exclusion was recently

reported in seven of 1067 patients treated by an AneuRx device (Medtronic, Santa Rosa, CA, USA)²⁶. The mean interval between treatment and operation was 16 months. Although endoleaks were diagnosed in only two of these patients, poor fixation of the graft proximally, distally and at the iliac junction was found to be the cause of rupture in all patients.

Transabdominal interventions with preservation of endograft function included an iliofemoral bypass, and treatment of endoleaks by clipping or direct ligation of side branches. Periaortic banding for a proximal endoleak¹³ was not applied to any patient in this study; it has been reported in EUROSTAR patients with shorter follow-up who were not included in this review.

Secondary femorofemoral crossover bypass was almost invariably undertaken for unilateral iliac limb occlusion. Late graft limb stenosis or thrombosis may be due to increased angulation and kinking secondary to distortion of the device. This is caused by shrinkage of the excluded aneurysm in transverse and longitudinal directions^{27,28}. While a significant correlation was found between iliac limb occlusion and extra-anatomic bypass, kinking was observed in only four of 21 patients. A possible explanation for this discrepancy may be that angulation and kinking is not easily diagnosed on routine planar CT. Angiography, spiral CT combined with multiplanar reconstruction and magnetic resonance angiography are the optimal imaging methods for visualization of angulation²⁹. However, these techniques were not applied universally in the EUROSTAR series. Another possible reason for the reported low incidence of angulation of the endograft is that thrombosis of the limb was often diagnosed and repaired on the basis of clinical assessment alone, without the addition of imaging. The finding that the RR of extra-anatomic bypass with image-detected limb occlusion was 5.6, while that for clinically diagnosed occlusion was as high as 37.5 is consistent with this explanation. It has been suggested that irregularity of the inner surface of the endograft due to the overlap of the component parts may be one cause of unilateral limb thrombosis^{17,30}. This association could not be investigated in the present study.

Transfemoral procedures constituted the most frequent category of secondary interventions. In the majority, these procedures consisted of aortic or iliac limb extension for migration or endoleak. Actual or impending disconnection of the separate iliac limb can be treated effectively by bridging the gap with another endograft. All abnormal findings on imaging surveillance that were investigated, including endoleak of all types, thrombosis/stenosis and kinking of the endograft, were seen significantly more frequently in patients with late endovascular procedures. This emphasizes the importance of a previous observation

by Hölzenbein *et al.*³¹ that most late adverse events can be resolved by appropriate endovascular techniques. The same authors pointed out that these secondary interventions are associated with low morbidity and mortality rates. In addition to the placement of extension endografts, the present transfemoral interventions included bare stenting (for kinking or stenosis), angioplasty (for type III connection endoleaks, graft wrinkling and stenotic segments) and coil embolization (for type II endoleak). Thrombolytic treatment of thrombosed iliac limbs, although a viable treatment option, was not used in any patient in this series.

An analysis of the data of a multicentre registry such as the EUROSTAR has a number of limitations. The data of approximately one-quarter of the patients were enrolled retrospectively. Several imaging techniques were used during follow-up; CT was used in two-thirds. Institutions with various experiences, using different device labels, participated. However, the findings of this study were interesting and perhaps reflected better the current outcome of EVAR than the experience of a single institution. Secondary intervention after EVAR is a relatively frequent event, in this series involving 18 per cent of the patients. In comparison, secondary interventions after open AAA repair are less frequent. Hallett *et al.*³² observed late graft-related complications requiring secondary operations in 6.8 per cent after a mean follow-up of 5.8 years. These complications involved anastomotic aneurysms, graft thrombosis, graft-enteric fistula and graft infections. This finding has considerable implications. First, patients need to be informed about the risk of complications that may necessitate secondary intervention. Second, reinterventions contribute to the costs of EVAR, although Patel *et al.*³³ found that the incremental costs caused by additional late procedures did not change the overall cost-effectiveness of the procedure. Finally, overall secondary interventions were associated with a slightly higher probability of death in the years following the primary procedure, although late death in this series was more often from causes unrelated to the aneurysm.

Secondary interventions are important determinants of late outcome and should be reported in detail in any study on clinical experience with endovascular AAA repair. In the EUROSTAR series to date they have been required at a constant rate of approximately 10 per cent per annum, throughout the intermediate and late follow-up periods. Lifelong patient surveillance, using accurate imaging techniques, is essential after EVAR.

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Gender differences in the longitudinal pressure profile of the anal canal related to anatomical structure as demonstrated on three-dimensional anal endosonography

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Background: Anal canal squeeze pressure is assumed to be due to external sphincter contraction, but the contribution of other muscles has not been explored.

Methods: Ten male and ten nulliparous female asymptomatic subjects had three-dimensional anal endosonography and manometry. Incremental squeeze pressures at 0.5-cm intervals, expressed as a percentage of the maximum pressure recorded anywhere in the canal, were related to the following anatomical levels: puborectalis, overlap between external anal sphincter (EAS) and puborectalis, external and internal anal sphincters, and external anal sphincter only. Levels were determined by coronal and sagittal endosonographic reconstructions.

Results: Puborectalis was the same length in men and women (median 23.9 *versus* 27.1 mm) but represented a greater proportion of the anal canal in women (45 *versus* 61 per cent; $P = 0.02$). At the level of puborectalis alone, the pressure generated as a proportion of maximum anal canal pressure was 71 (range 32–100) per cent in men and 62 (range 32–100) per cent in women. At the level of the EAS alone, the pressure was 60 (4–98) per cent in men and 82 (41–100) per cent in women; where the external sphincter was overlapped by puborectalis, the pressure was 98 (60–100) per cent in men and 75 (47–100) per cent in women.

Conclusion: Maximal anal canal squeeze pressure is found where the puborectalis overlaps the EAS. This segment represents a significant proportion of anal canal length in women.

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Introduction

The resting tone of the anal canal has been attributed mainly to tonic contraction of the internal anal sphincter (IAS)^{1,2}, with some contribution from the external anal sphincter (EAS) and soft tissue of the anal canal³. The striated muscle of the EAS generates maximal voluntary squeeze pressure⁴. The other striated muscle component of the pelvic floor that is intimately related to the external sphincter is the puborectalis. This forms a sling around the anorectal junction, pulling it forward, a function that has

been suggested to play a part in maintaining continence^{5,6}. To what extent the puborectalis contributes to resting and squeeze pressures in the anal canal has not been established.

Anal manometry using either a station pull-through technique or vector volume analysis records the pressure profile along the anal canal both at rest and during an active squeeze^{7,8}. The site and length of the high-pressure zone and the pressure changes both at rest and during straining can be measured using the anal verge as a reference point.

Endosonography of the anal canal⁹ is usually imaged in the axial plane¹⁰. Three-dimensional anal endosonography (AES) has enabled images of the anal canal to be reconstructed in the coronal and sagittal planes^{11,12}. Using this technique it is possible to map the location and dimensions of sphincteric components along the length of

The Editors have satisfied themselves that all authors have contributed significantly to this publication

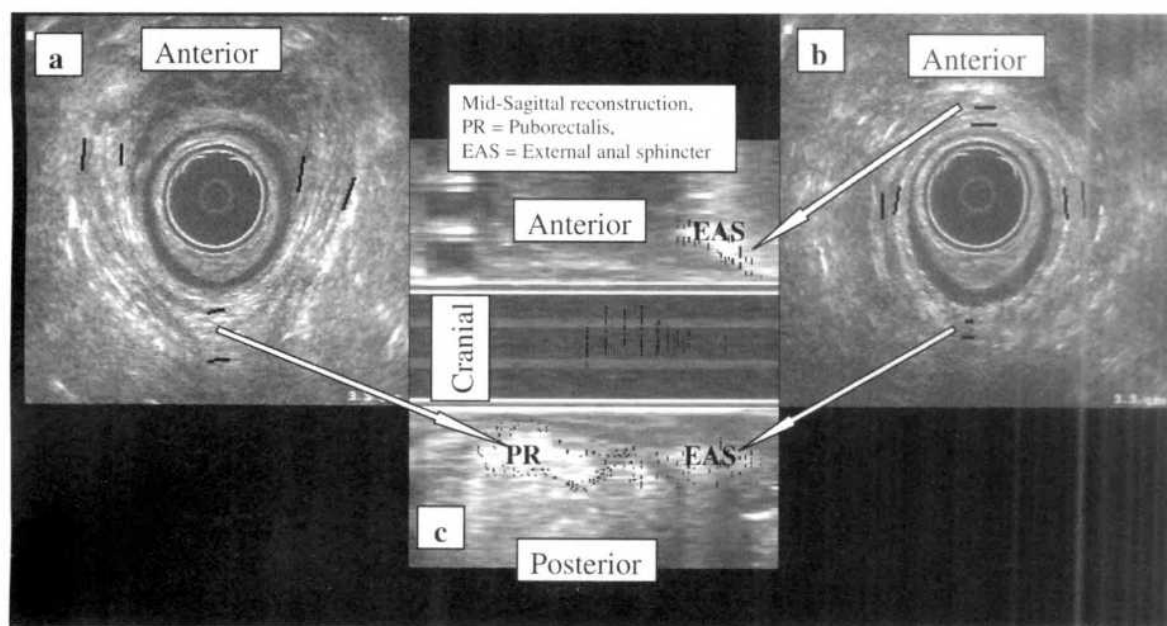


Fig. 1 Structures of the anal canal as seen on three-dimensional anal endosonography. **a** Axial slice with borders of puborectalis (PR) outlined at 3, 6 and 9 o'clock. **b** Axial slice with borders of external anal sphincter (EAS) outlined at 3, 6, 9 and 12 o'clock. **c** Mid-sagittal reconstruction. Arrows indicate how the individual markings in each axial slice translate into the volume of data. When sliced, these marks outline the structures of interest

the anal canal and to make direct comparisons with the pressure generated by each component.

Methods

Ten male and ten nulliparous female age-matched volunteers with no history of anal surgery or incontinence were recruited and informed written consent was obtained. Ethical approval had been granted from the Harrow research ethics committee. Each patient underwent AES and anal manometry on the same day.

Three-dimensional anal endosonography

Three-dimensional AES was performed using a Brüel and Kjær Medical (Sandhoften, Denmark) ultrasound scanner type 3535 with a 10-MHz rotating rectal probe. The technique has been described previously¹¹. The anal margin was recognized by the reverberation echo that forms when the transducer loses contact with the caudal anal canal.

The data volume was viewed in the software program used for three-dimensional reconstruction (Vaytek, Fairfield, Iowa, USA) in the axial plane. The caudal and cranial terminations of the IAS, EAS and puborectalis were

marked in the 12 and 6 o'clock positions in the axial plane (Fig. 1a). The medial and lateral borders of the external sphincter and the puborectalis were also marked at the 6, 9 and 12 o'clock positions (Fig. 1b). These marks were fixed within the data volume and appeared whenever the plane that was being viewed passed through them. In the mid-sagittal and mid-coronal reconstructions, these marks outlined the perimeter of the muscular components; the 12 and 6 o'clock markers were reproduced in the sagittal plane, and the 9 o'clock markers in the coronal plane, allowing delineation of the muscular components of the canal (Fig. 1c). Taking the reverberation echo as the fixed point of the anal verge, the volume was marked at 0.5-cm intervals along the length of the canal to provide fixed points so that the images could be matched with manometric data.

The lengths of the external and internal sphincters and of the puborectalis were measured by means of a medical imaging computer package (Scion Image; Scion Corporation, Frederick, Maryland, USA). The anatomical canal length was measured from the most cranial part of puborectalis posteriorly to the anal verge. The EAS was measured anteriorly and posteriorly in the sagittal reconstruction, and in the mid-coronal reconstruction. The puborectalis was measured posteriorly in the mid-sagittal reconstruction. The IAS was measured in the mid-coronal

plane. The percentage of the total anal canal length that each structure occupied was then calculated.

Manometry

The mean maximal resting pressure and mean maximal incremental squeeze pressure (the rise above mean maximal resting pressure on maximal voluntary squeeze) were recorded at 0.5-cm intervals, starting at 6 cm from the anal verge. This was performed using a station pull-through technique (0.5-cm stations) with a radially arranged eight-channel, water-perfused (0.5 ml/min) manometry catheter. Pressures were allowed to equilibrate after each change in station for not less than 2 min. The pressures were averaged at each position and converted to a percentage of the maximum pressure found anywhere along the anal canal for both resting and maximal incremental squeeze pressures.

The functional length of the anal canal was taken from the point where mean maximal resting pressure was 20 per cent or more of the maximum resting pressure anywhere along the anal canal (corresponding approximately to a rise of 10 cmH₂O above rectal pressure) to the anal verge. The high-pressure zone was defined as the length of the canal where mean maximal resting pressure was 50 per cent or more of the maximum resting pressure at any point along the canal¹³.

The manometric pressures at 0.5-cm intervals from the anal verge were then mapped on to the three-dimensional AES reconstructions so that the corresponding anatomical structures present at each level could be determined. The percentage of maximum resting and squeeze pressures that corresponded with the following anatomical levels were also recorded: rectum, puborectalis alone, puborectalis overlapping external (deep) and internal sphincters, external (superficial) and internal sphincter, external (subcutaneous) sphincter alone.

Statistical analysis

The pressure data were not normally distributed, so the Mann–Whitney *U* test was used for comparisons between the sexes. Where comparisons between anterior and posterior components of the sphincter were made, paired *t* tests were employed. Values are given as median (range) unless stated otherwise. $P < 0.05$ was considered statistically significant. Analysis was performed with Arcus Quickstat Biomedical[®], version 1.2 (Research Solutions, Cambridge, UK).

Results

The two subject groups were of similar age: men 31.4 (range 24–44) years; women 31.3 (range 20–48) years.

Gender differences in anal canal anatomy

The differences in anal canal anatomy between men and women are shown in *Table 1*. The anal canal was significantly longer in men than in women, as a result of a longer EAS. There was no difference in puborectalis length. There was no asymmetry of the external sphincter in the sagittal plane, with no significant difference between anterior and posterior EAS lengths in either men or women. However, the anterior EAS occupied 58 per cent of the male anal canal compared with 38 per cent of the female canal ($P < 0.01$). In women the puborectalis occupied a significantly larger proportion of the canal than in men (61 *versus* 45 per cent; $P = 0.02$).

There was no difference in the length of the IAS between men and women (34.4 (range 30.6–37.4) *versus* 33.2 (range 22.5–41.3) mm; $P = 0.72$) or the proportion of the anal canal that it occupied (67 *versus* 73 per cent; $P = 0.12$).

Sex differences in manometry

There was no difference in the maximal resting pressure between men and women (97 (range 55–136) *versus* 79 (range 58–135) cmH₂O; $P = 0.24$); however, men had significantly higher maximal incremental squeeze pressures than women (185 (range 61–287) *versus* 110 (range 38–143) cmH₂O; $P = 0.02$). The pressure profiles for resting and squeeze pressures along the anal canal, together with a graphic representation of the canal anatomy, are shown in *Figs 2–5*. The median functional canal length was 4.0 (range 2.5–5.0) cm in men and 3.8 (range 2.0–4.5) cm in women. The median high pressure zone length was longer in men than in women (3.0 (range 2.5–4.0) cm *versus* 2.5 (range 1.5–3.0) cm; $P = 0.03$), which can be seen by the 50 per cent intersect on *Figs 2* and *4*.

The percentage maximum pressure associated with the location of each of the anatomical structures was recorded

Table 1 Gender differences in the anatomy of the anal canal

	Length (mm)		<i>P</i> *
	Men	Women	
Anatomical canal	50.2 (44.5–58.9)	42.2 (35.8–60.0)	0.019
Puborectalis (postsagittal)	23.9 (15.7–38.5)	27.1 (20.1–29.3)	0.49
Anterior EAS (sagittal)	30.1 (24.1–36.1)	15.6 (7.9–37.1)	<0.001
EAS (coronal)	31.6 (26.2–36.4)	19.5 (12.3–34.3)	<0.001
Posterior EAS (sagittal)	29.3 (22.5–35.8)	16.5 (9.7–41.3)	0.002
IAS (coronal)	34.4 (30.6–37.4)	33.2 (22.5–41.3)	0.72

EAS, external anal sphincter; IAS, internal anal sphincter. $P = 0.28$ (female EAS anterior *versus* posterior length); $P = 0.43$ (male EAS anterior *versus* posterior length) (Wilcoxon signed rank test). *Mann–Whitney *U* test

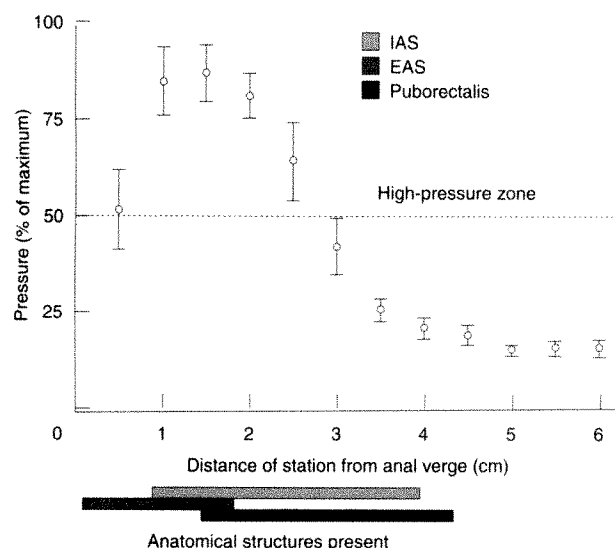


Fig. 2 Resting pressures for women by station. Values are mean(s.e.m.). IAS, internal anal sphincter; EAS, external anal sphincter

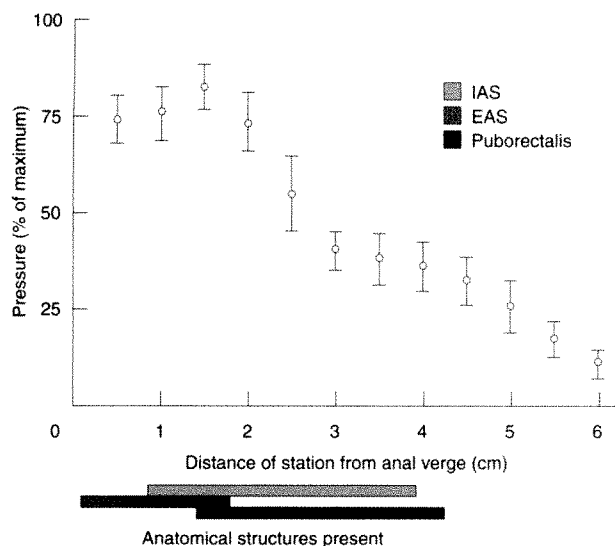


Fig. 3 Squeeze pressures for women by station. Values are mean(s.e.m.). IAS, internal anal sphincter; EAS, external anal sphincter

for both resting and squeeze pressure, and the results are shown in *Table 2*. The maximal resting pressure for both men and women occurred where the external and internal sphincters overlapped. The high-pressure zone in both men and women extended caudally beyond the distal termination of the IAS, and the area where only the EAS was present was associated with resting pressures that were 87 per cent of maximum in men and 76 per cent of maximum in women.

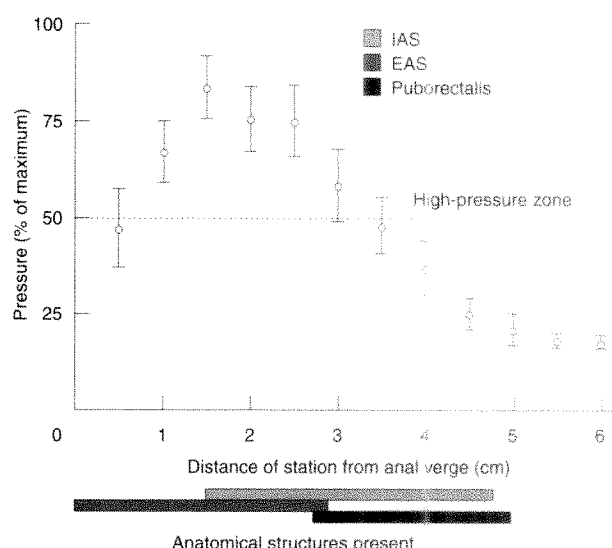


Fig. 4 Resting pressures for men by station. Values are mean(s.e.m.). IAS, internal anal sphincter; EAS, external anal sphincter

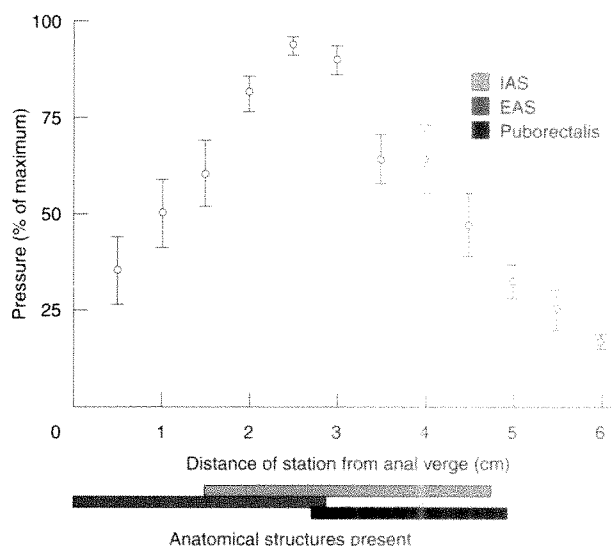


Fig. 5 Squeeze pressures for men by station. Values are mean(s.e.m.). IAS, internal anal sphincter; EAS, external anal sphincter

The maximum resting pressure in both men and women was found at the caudal termination of the IAS. The upper extent of the high-pressure zone in both sexes was caudal to the most cranial extent of the IAS; however, the start of the functional anal canal (rise above rectal pressure) occurred at the upper extent of the internal sphincter.

Squeeze pressure was maximal in men at the level of the EAS–puborectalis overlap, whereas in women the location

Table 2 Contribution of anatomical structures to resting and squeeze pressures

	Resting pressure (% of maximum)			Squeeze pressure (% of maximum)		
	Men	Women	<i>P</i> *	Men	Women	<i>P</i> *
Puborectalis alone	42 (19–72)	40 (25–98)	0.47	71 (32–100)	62 (32–100)	0.67
Puborectalis, EAS and IAS	68 (7–100)	95 (33–100)	0.21	98 (60–100)	75 (47–100)	0.32
EAS and IAS	99 (44–100)	100 (40–100)	0.97	91 (52–100)	94 (51–100)	0.86
EAS alone	67 (13–100)	66 (24–100)	0.69	60 (4–98)	82 (41–100)	0.10

Values are median (range). EAS, external anal sphincter; IAS, internal anal sphincter. *Mann–Whitney *U* test

of maximal squeeze was more caudal, below the termination of the puborectalis where only external and internal sphincters were present. The region where only distal EAS was present was associated with 60 per cent of maximum squeeze pressure in men and 82 per cent in women ($P=0.1$).

In men there was no significant difference between squeeze pressure at the level of puborectalis with or without EAS overlap. The pressure at the level where only the external sphincter was present was significantly lower than that at the level where the EAS overlapped either puborectalis (60 *versus* 98 per cent; $P<0.01$) or the IAS (60 *versus* 91 per cent; $P<0.01$). In women, while squeeze pressure at the level of puborectalis was significantly lower than that at the level where the EAS overlapped the IAS (62 *versus* 94 per cent; $P=0.04$), it did not differ significantly from pressures at any other level.

Discussion

Gender difference in anal canal length has been shown to be due to a longer EAS in men. Previous reports have suggested that the external sphincter is shorter anteriorly in women¹¹, but in this study the EAS was found to be sagittally symmetrical, although comprising a greater extent of the total anal canal length in men than in women. The absolute measurements were similar to those in the previous report¹¹, and the discrepancy is due to better discrimination between the EAS and puborectalis posteriorly.

The contribution of tonic contraction of the IAS to resting anal canal pressure is thought to be between 50 and 85 per cent^{1,2,14,15}. The striated muscles and soft tissues are responsible for the remainder of the resting anal canal pressure⁷. However, the location of the internal sphincter was found not to correspond exactly to the high-pressure zone. The IAS starts above the cranial extent of the high-pressure zone and finishes above the caudal termination of the zone. From *Figure 2* and *Figure 4* it can be seen that in women, the internal sphincter was present in 80 per cent of

the high-pressure zone, but in men in only 66 per cent. The striated muscles of the anal canal therefore seem likely to contribute significantly to the resting anal canal pressure. This is supported by Wong *et al.*¹⁶, who found that resting pressure correlated with the combined area of the internal and external sphincters, and not solely with that of the IAS. Where the EAS was the sole sphincteric component, the resting pressure was 67 per cent in men and 66 per cent of maximum in women. High in the anal canal there is radial asymmetry of resting pressure^{8,17}. The relatively higher posterior pressures have been attributed to the puborectalis, which forms a sling around the anorectal junction but is deficient anteriorly. However, as the IAS always overlapped the puborectalis, the function of these components could not be separated in the present study.

Voluntary squeeze pressure is generated by the striated muscular components of the anal canal, which are constantly at a low state of excitation^{1,18}. The puborectalis muscle elevates and angulates the anorectal junction¹⁹. It is not believed to contribute to anal squeeze pressure²⁰ as it does not encircle the anal canal. However, patients with faecal incontinence due to anal sphincter trauma often have anal squeeze pressure preserved high in the anal canal¹⁹. More evidence for a sphincteric role derives from division of the puborectalis for the treatment of chronic constipation, as this leads to a high rate of incontinence to flatus and mucus²¹.

The puborectalis occupies a greater proportion of the length of the anal canal in women, and above the external sphincter was associated with 71 per cent of maximum anal squeeze pressure in men and 62 per cent in women. This pressure is directly attributable to the puborectalis in the absence of other striated muscles in this region and any effect from the IAS is automatically subtracted by recording incremental anal squeeze pressures (i.e. rise above resting pressure). It could be argued that this pressure rise on active squeezing simply reflects transmitted pressure from an increase in intra-abdominal pressure. If the station pull-through is repeated, asking the subject to cough maximally at each station, then a pressure profile is obtained that is

different from the maximal anal squeeze trace. The most cranial pressure readings are of intrarectal pressure, which are higher during a maximal cough than during maximal squeeze owing to the transmitted intra-abdominal pressure. Pressures recorded during a cough at the level of puborectalis are the same as those found during maximal anal squeeze, being due to reflex striated muscle contraction and not to an increase in abdominal pressure.

The area of maximum squeeze occurred at the level where puborectalis overlaps the EAS in men and just distal to the termination of puborectalis in women, suggesting synergy in the function of these muscle groups. The subcutaneous external sphincter was longer in men and associated with 60 per cent of maximal squeeze pressure, compared with 82 per cent in women. These findings have implications for anal sphincter surgery. In men division of the subcutaneous external sphincter may be without functional effect, whereas in women the shorter subcutaneous EAS division could have a significant effect on continence. In women division of the external sphincter anteriorly has to extend only a short distance above the IAS for the entire anal sphincter to be divided, with dramatic reduction in faecal continence.

Demonstration of a sphincteric effect of the puborectalis may explain why, anecdotally, some patients are seen who are continent with extensive EAS trauma but an intact puborectalis. At present, all attention at the time of surgical repair for obstetric sphincter injury is addressed to overlapping the torn ends of the external sphincter. If the puborectalis has a functional role in closing the anal canal, the results of anal sphincter repair may be more dependent upon the ability of puborectalis to compensate for a damaged lower sphincter. Pelvic floor denervation may result in atrophy of puborectalis, thus impairing its ability to compensate for lower sphincter injury.

Acknowledgements

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Endorectal flap advancement repair and fistulectomy for high trans-sphincteric and suprasphincteric fistulas

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Background: Low-lying trans-sphincteric anal fistulas respond well to simple fistulectomy or fistulotomy. However, management of high fistulas has long been a serious problem because of the necessity of preserving at least some of the sphincter mechanism. The clinical results of endorectal flap advancement and fistulectomy for complex anal fistulas were assessed.

Methods: A total of 103 consecutive patients with high trans-sphincteric ($n = 91$) and suprasphincteric ($n = 12$) fistulas undergoing endorectal advancement flap repair together with core fistulectomy were included in a prospective study. Clinical outcome was assessed in terms of continence and recurrence by an independent observer for a period of 1 year after operation.

Results: Successful healing was achieved in 96 patients (93 per cent). Recurrent fistula occurred in six (7 per cent) of the 91 patients in the trans-sphincteric group and in one of the 12 patients in the suprasphincteric group. Continence disturbance was noted in eight patients (8 per cent). Previous repair and the level of the fistula did not adversely affect the results obtained.

Conclusion: Core fistulectomy associated with endorectal advancement flap repair is a safe and effective technique for any high trans-sphincteric and suprasphincteric fistula, with good results in terms of recurrence and anal continence.

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Introduction

The goal of surgical treatment of anal fistulas is to cure the disease without compromising faecal continence. Traditionally, high fistulas have been treated by a number of techniques, including a staging procedure or seton applications, but reported results indicate a high incidence of incontinence and recurrence of the fistula¹. Excision of the fistula tract and repair of the primary defect with advancement of rectal flap fulfils the necessary criteria for cure and preservation of the normal anatomy and function of the anal canal. Good results using this technique have been reported in different studies published in the literature^{2–5}. Unfortunately, most series on endorectal advancement flap technique are small and heterogeneous or have not included accurate data on long-term success and safety^{2–5}. To investigate the frequency of recurrence and faecal incontinence associated with this surgical technique, a prospective study was carried out of all consecutive patients with high trans-sphincteric and suprasphincteric fistulas operated on over an 18-month period and followed for 1 year.

Patients and methods

Between 1 May 1997 and 30 November 1998, 118 consecutive patients diagnosed with high trans-sphincteric or suprasphincteric fistula of cryptoglandular origin underwent fistulectomy and endorectal advancement flap repair. Fifteen patients (13 per cent) in whom the internal opening could not be located, and who were therefore unsuitable for a transanal rectal advancement flap, were excluded from the study. Thus, the study population consisted of 103 patients (76 men and 27 women) with a median age of 45 (range 19–76) years. Fifteen patients (15 per cent) had previously undergone one or more attempts at repair before referral to the authors' hospital.

Before operation every patient underwent a digital examination, proctosigmoidoscopy (rigid or flexible) and rectal endosonography. All operations were performed by the same surgeon (H.O.). The anatomical location of fistulas according to the criteria of Parks *et al.*⁶ is shown in Table 1. Fistulas were trans-sphincteric in 91 patients (88 per cent) and suprasphincteric in 12. The tract passed across

Table 1 Type of fistula and anatomical location in 103 patients undergoing endorectal advancement flap repair

Data	No. of patients
Type of fistula	
Suprasphincteric	12 (12)
Trans-sphincteric*	91 (88)
Internal opening	
Lateral	14 (14)
Midline anterior	36 (35)
Midline posterior	53 (51)
Extension	
Vertical	34 (33)
Horizontal	21 (20)
Horseshoe	7 (7)
Previous fistula surgery	15 (15)

Values in parentheses are percentages. *The tract passed across the upper third in 13 and across the middle third in 78.

the upper third of the external sphincter in 13 patients and across the middle third in 78.

Operation was delayed until symptoms of acute inflammation subsided. All patients underwent mechanical bowel preparation and received antibiotic and antithromboembolic prophylaxis. With the patient in the lithotomy or jack-knife position, depending on the location of the internal opening, the main fistulous tract and any secondary tracts running from the external opening to the anal canal were dissected. A small elliptical incision around the internal opening was made and the fistula tract was then excised. The internal and external openings were sutured with interrupted 4/0 polyglactin sutures (Ethicon Endosurgery, Madrid, Spain). A curvilinear (semicircular) flap consisting of mucosa, submucosa and a few muscular fibres was raised immediately above the internal opening and mobilized 4–6 cm proximally. The base of the flap was approximately twice the width of its apex. The flap was advanced and sutured (also with 4/0 polyglactin) to the level of the intersphincteric line. The external wound was left open for drainage and packed loosely. After operation, intravenous fluid replacement therapy was maintained for 5 days followed by normal diet and use of bulk laxatives. Anal cleansing was done with sitz baths after bowel movement. The external wound was dressed daily. Each patient was seen every 2 weeks until the wound healed.

An independent observer assessed continence and recurrence at follow-up. The degree of incontinence was scored on a scale of 1–18 according to the incontinence score system of Miller *et al.*⁷ and evaluated before operation and 1 year after operation. Patients were examined at 3-month intervals in the outpatient clinic to determine recurrence. Recurrence was defined as a discharge or abscess arising in the same area, or by obvious evidence of fistulation.

Table 2 Continence 1 year after operation in 101 patients with normal continence status before operation

Degree of incontinence ⁶	Flatus	Fluid	Solids
Grade I	1†	2‡	1‡
Grade II	1† 2‡	—	—
Grade III	1‡	—	—

Grade I, less frequent than once a month; grade II, incontinent episodes between once a month and once a week; grade III, incontinent episodes more than once a week. †Suprasphincteric; ‡trans-sphincteric.

Fisher's exact probability test was used for analysis of data; $P < 0.05$ was considered statistically significant.

Results

Recurrent fistula occurred in seven of the 103 patients, giving an overall recurrence rate of 7 per cent: six (7 per cent) of 91 patients in the trans-sphincteric group and one of 12 in the suprasphincteric group (risk ratio (RR) 1.02 (95 per cent confidence interval (c.i.) 0.85–1.22), $P = 0.59$, two-tailed Fisher's exact test). There were no statistically significant differences in recurrence rate between patients who had had previously undergone attempts at repair before referral to the authors' institution (two of 15) and those operated on for the first time (five (6 per cent) of 88) (RR 1.09 (95 per cent c.i. 0.89–1.34), $P = 0.26$, two-tailed Fisher's exact test).

Continence disturbance related to the operation is showed in Table 2. In two patients there was no change in continence to flatus (grade II, incontinent episodes between once a month and once a week) before and after operation. Of the remaining 101 patients who had normal continence status before operation, eight (six of 99) (six in the trans-sphincteric group and two in the suprasphincteric group) complained of continence disturbance attributable to the operation. Differences in the rate of incontinence according to type of fistula (trans-sphincteric, six of 99; suprasphincteric, two of 12) were not statistically significant (RR 1.12 (95 per cent c.i. 0.86–1.45), $P = 0.24$, two-tailed Fisher's exact test).

Discussion

As far as the authors are aware, this is the first prospective series of endorectal advancement flap repair of high anal fistula (any fistula that involves a significant amount of the sphincter mechanism) in which most patients had not previously been operated on. For this reason it is difficult to compare the present results with those reported by other authors using the so-called 'transanal rectal advancement

flap'. In the largest series published in the literature, Aguilar *et al.*³ reported using a similar technique to treat 189 patients with anal fistula with a recurrence rate of 1.5 per cent, compared with the failure rate of 7 per cent in the present study. The fact that fistula type was not mentioned in the study of Aguilar *et al.*³ may account for the difference. On the other hand, 10 per cent of their patients had symptoms of incontinence (8 per cent in the present series), although they did not report how many patients complained of continence disturbance before operation. Complaints about disorders of continence are common presenting symptoms in patients previously operated on for fistula *in-ano*^{8,9}.

In the excellent review of Kodner *et al.*², describing patients treated by endorectal advancement flap repair over a 10-year period, there is no description of the fistulectomy procedure for those with perianal fistula. Thirty-one patients with cryptoglandular abscess-fistula were operated on, with a recurrence rate of 13 per cent. Unfortunately, data on continence were not recorded. As pointed out by Schouten *et al.*⁹, the use of a Parks' retractor to gain exposure may cause overstretching of the sphincters during operation, contributing to the impairment of continence.

Results of endorectal advancement flap repair in patients with anal fistula collected from the literature are shown in Table 3. It should be noted that in the two studies with the highest recurrence rates (25 and 32 per cent)^{9,10} poor outcome was attributed to the fact that most patients had undergone previous operations. In the experience of Schouten *et al.*⁹, success was inversely correlated with the number of previous attempts, i.e. healing rate of 87 per cent in patients with no or one previous attempt at repair, compared with 50 per cent in patients with two or more previous repairs. In agreement with these findings, Ozuner *et al.*¹⁰ reported statistically higher recurrence rates in patients who had undergone previous repairs, although rectovaginal fistulas, complex anorectal fistulas and high rectourethral fistulas in association with Crohn's disease

were included in this study and individualized values for fistula type are not given. By contrast, in the present series of patients with cryptoglandular trans-sphincteric and supra-sphincteric fistulas, patients who had undergone previous operations did not have a less favourable outcome.

Results of the present study in terms of recurrence and continence disturbance are apparently more favourable than those reported previously, particularly in relation to continence status after the staged cutting seton technique. Garcia-Aguilar *et al.*¹¹, who treated patients mostly by fistulectomy, reported a recurrence rate of 7 per cent for trans-sphincteric fistulas (including low-lying fistulas) and 33 per cent for suprasphincteric fistulas. With regard to incontinence, rates varied between 54 per cent for trans-sphincteric fistulas (55 per cent for those with 51–75 per cent involvement of the external sphincter, 75 per cent for those with more than 76 per cent involvement) to 80 per cent for suprasphincteric fistulas. In a recent study on the use of seton techniques in the surgical management of high anal fistula, these authors¹² reported a recurrence rate of 8 per cent and continence disturbance of 66 per cent (stool incontinence 25 per cent).

In summary, fistulectomy associated with endorectal flap repair is a safe and effective technique for high trans-sphincteric and suprasphincteric fistulas, with satisfactory results in terms of recurrence and anal continence.

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Table 3 Recurrence rates and incidence of disturbed continence after fistulectomy and endorectal advancement flap repair in patients with high fistulas of cryptoglandular origin

Reference	Year	No. of patients	Follow-up	Recurrence rate (%)	Incontinence rate (%)
Oh ⁴	1983	15	—	13	—
Aguilar <i>et al.</i> ³	1985	151	8 months to 7 years	2	10
Wedell <i>et al.</i> ⁶	1987	27	18 months to 4 years	0	0
Kodner <i>et al.</i> ²	1993	31	7 months	13	—
Ozuner <i>et al.</i> ¹⁰	1996	19	31 months (median)	32	—
Miller and Finan ⁵	1998	18	14 months (median)	17	0
Schouten <i>et al.</i> ⁹	1999	44	12 months (median)	25	35
Present study	2000	103	12 months	7	8

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Mitogenic effects of oestrogen mediated by a non-genomic receptor in human colon

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Background: Oestrogens are important mitogens in epithelial cancers, particularly where tumours express complementary receptors. While the traditional model of oestrogen action involves gene-directed (genomic) protein synthesis, it has been established that more rapid, non-genomic steroid hormone actions exist. This study investigated the hypothesis that oestrogen rapidly alters cell membrane activity, intracellular pH and nuclear kinetics in a mitogenic fashion.

Methods: Crypts isolated from human distal colon and colorectal cancer cell lines were used as robust models. DNA replication and intracellular pH were measured by radiolabelled thymidine incorporation (12 h) and spectrofluorescence imaging respectively. Genomic protein synthesis, sodium-hydrogen exchanger (NHE) and protein kinase C (PKC) activity were inhibited with cycloheximide, ethylisopropylamiloride and chelerythrine chloride respectively.

Results: Oestrogen induced a rapid (less than 5 min) cellular alkalinization of crypts and cancer cells that was sensitive to NHE blockade ($P < 0.01$) or PKC inhibition ($P < 0.01$). Oestrogen increased thymidine incorporation by 44 per cent in crypts and by up to 38 per cent in cancer cells ($P < 0.01$), and this was similarly reduced by inhibiting the NHE ($P < 0.01$) or PKC ($P < 0.05$).

Conclusion: Oestrogen rapidly activates cell membrane and nuclear kinetics by a non-genomic mechanism mediated by PKC but not gene-directed protein synthesis.

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Introduction

Oestrogen has been linked inextricably to the pathobiology of breast cancer; the sex hormone receptor status of the tumour is an important determinant of adjuvant therapy and prognosis¹. There is a well described association between breast cancer and extramammary neoplasms, including colorectal carcinoma^{2,3}. Women under 55 years of age have a higher incidence of colorectal cancer than men and this relationship reverses following menopause^{4–6}. Such epidemiological data suggest a role for oestrogens in the pathogenesis of large bowel cancer. However, hormone replacement therapy confers a protective effect against hindgut malignancy^{7–9}. These seemingly contradictory statistics have been attributed to the differing mitogenic properties of oestradiol, the naturally produced active hormone, and the pharmacological preparations (e.g. oestrone)¹⁰. Oestradiol stimulates, while oestrone inhibits, colon cancer cell growth^{10,11}. Peripheral conversion of oestradiol to the less potent oestrone (by 17 β -hydroxy-

steroid dehydrogenase) is significantly lower in colonic tumours than in normal mucosa¹⁰. Thus the bioavailability of oestradiol is higher in the microenvironment of the cancer than the surrounding tissue.

Similar to many epithelial malignancies, most human colon cancers express intracellular (nuclear and cytoplasmic) receptors that exhibit biological responses to oestrogen^{12–16}. Recent evidence suggests that colonic carcinoma cell growth is stimulated by oestradiol in a mechanism dependent on such receptors¹¹. In support of this, oophorectomy retards large bowel tumour growth in animal studies and antioestrogen compounds inhibit colon cancer cell proliferation *in vitro*^{17–19}. Curiously, these effects of antioestrogen agents were in cell lines that may bind oestradiol yet do not express classical, intracellular oestrogen receptors^{10,18,19}. Therefore, it has been speculated that the effects of oestrogen (or oestrogen-like molecules) are mediated via non-classical receptors¹⁰.

A new concept of steroid hormone action has been emerging that proposes two distinct signal transduction

mechanisms. The classical receptors conform to the traditional 'genomic' concept including ligation of an intracellular domain, translocation to the nucleus, and a latent period (more than 60 min) during which gene-directed protein synthesis occurs²⁰. A second, 'non-genomic' pathway, which exhibits temporal and spatial segregation from the genomic receptor mechanism, has been identified²¹⁻²⁵. It is rapidly responsive and involves membrane-associated signal transduction mechanisms (independent of protein synthesis)²¹⁻²⁵.

Steroid hormones (including oestrogen) exert rapid, non-genomic effects on solute transport in mammalian colon²¹⁻²³. Non-genomic second messenger signals, including protein kinase C (PKC), have been identified in rat colon and colon cancer cell lines^{24,25}. Endogenous growth factors and carcinogenic agents (e.g. phorbol esters) evoke PKC-mediated activation of a specific ion exchange mechanism in the plasma membrane of many cell types²⁶. The transfer of extracellular sodium for intracellular hydrogen ions by this sodium-hydrogen exchanger (NHE) induces the cytoplasmic alkalization necessary for growth stimulation^{26,27}. The hypothesis that oestrogens activate the NHE non-genomically and thus exert mitogenic influences in human colonic tissue was examined in this study.

Patients and methods

Tissue and cell preparation

Samples of normal human colon were obtained from freshly resected colectomy specimens and transferred immediately to the laboratory in preoxygenated Ringer's solution. Samples of mucosa were obtained by microdissection, crypts were isolated by chemodissection, and intracellular pH was measured by spectrofluorescence as described previously²¹⁻²³. In brief, colonic crypts were freed from the mucosal stroma by exposure to a calcium chelation solution of pH 7.4 (sodium chloride 96 mmol/l, potassium chloride 1.5 mmol/l, Hepes/Tris 10 mmol/l, disodium ethylenediamine tetra-acetic acid 27 mmol/l, sorbitol 45 mmol/l and sucrose 28 mmol/l) and isolated by short-cycle, low-revolution centrifugation. Three colorectal cancer cell lines (T84, Caco2 and HCT15) were used as models of tumour kinetics. The HCT15 cell line has been noted previously to lack expression of the classical, genomic-mediated oestrogen receptors²⁸. Cancer cells were cultured and prepared as described previously²⁵. Crypts (or cancer cells) were suspended in a Hepes-buffered Ringer's solution at pH 7.4 (sodium chloride 140 mmol/l, potassium chloride 4.7 mmol/l, calcium chloride 2.5 mmol/l, magnesium sulphate 1.2 mmol/l, monopotassium phosphate 1.2 mmol/l, sodium Hepes 6.0 mmol/l and glucose 11.1 mmol/l).

Where indicated, the sodium concentration of the perfusate was reduced to zero by replacement with *N*-methyl-D-glucamine.

Spectrofluorescence imaging

Isolated crypts (or cancer cells) were attached to 24 × 40 mm coverslips in perfusion chambers and were incubated with 2',7'-bis-(2-carboxyethyl)-5,6-carboxy-fluorescein (BCECF)-acetoxymethyl ester 3 µmol/l at room temperature for 30 min. Cytoplasmic esterase hydrolyses the acetomethoxy group and traps the pH-sensitive, membrane-impermeant fluorescent dye BCECF in the cells. Dye-loaded crypts (or cancer cells) were imaged with an inverted epifluorescence microscope (Diaphot 200, Nikon, Tokyo, Japan). The light from a xenon lamp was filtered through alternating 440- and 480-nm interference filters. The emitted fluorescence was passed through a 400-nm dichroic mirror, filtered at 510 nm and then collected using an intensified camera. Images were digitized and analysed using the Starwise Fluo system (Imstar, Paris, France). Six regions of interest (containing four cells or more) were analysed in each crypt such that at least 24 cell recordings per crypt were acquired. Similarly, measurements from 20 or more cancer cells were acquired in each experiment.

DNA replication activity

DNA replication was assessed by measuring the uptake of radiolabelled thymidine as described elsewhere²⁸. In brief, cancer cells or crypts were placed in filtered multiwelled plates and exposed to [³H]thymidine in solution (5 µCi/ml) for 12 h. Plates were set at 0.8 bars on an Eppendorf Event 4160 vacuum (Eppendorf-Netheler-Hinz, Hamburg, Germany) and protein was precipitated by washing twice with 7.5 per cent trichloroacetic acid. Filters were placed in vials containing Ecolite scintillation cocktail (ICN Biomedicals, Costa Mesa, California, USA) and radioactive counts, indicating the degree of [³H]thymidine uptake, were measured with a scintillation counter.

Data analysis

Results were processed using a statistical software package (Statview, Abacus Concepts, Berkeley, CA, USA). Mann-Whitney *U* test was used for statistical analysis and *P* < 0.05 was considered significant. Results are presented as mean (s.e.m.) where *n* is the number of experiments. The use of human tissue was approved by the University Hospitals' Ethics Committee.

Results

The basal cytosolic pH recorded from the human colonic crypts was 7.22(0.02) ($n = 32$). Perfusion of the crypts with oestradiol (17β -oestradiol 1 nmol/l) induced a rapid change in pH within 1 min, which achieved statistical significance at 5 min (7.38(0.03); $n = 16$, $P < 0.01$). A plateau pH (7.40(0.03); $n = 16$, $P < 0.01$) was achieved within 9(2) min (Fig. 1). This represents a maximal pH change of 0.18(0.04) ($P < 0.01$). Similarly, oestradiol 1 nmol/l rapidly altered the intracellular pH of T84 cells (maximal pH change 0.21(0.02); $n = 32$, $P < 0.01$) and Caco2 cells (maximal pH change 0.14(0.03); $n = 12$, $P < 0.05$). However, oestradiol did not significantly alter the cytosolic pH of the oestrogen receptor-negative HCT15 cell line (basal pH 7.18(0.05); pH at 20 min 7.20(0.07); $n = 16$, $P > 0.1$). The concentration-dependence of oestradiol-mediated alkalinization of crypts and responding colon cancer cells was within a clinically relevant range (0.1–100 nmol/l). The half-maximal concentration of approximately 1 nmol/l was used in all subsequent experiments. A potent oestrogen antagonist (ICI 182 780 1 μ mol/l)¹¹ significantly inhibited the maximal pH shift induced by oestradiol in crypts (0.07(0.02); $n = 6$, $P < 0.01$), T84 cells (0.06(0.03); $n = 6$, $P < 0.01$) and Caco2 cells (0.03(0.01); $n = 6$, $P < 0.01$). None of the other steroid hormones tested, including progesterone, testosterone, and the oestrogenic compounds 17α -oestradiol and oestrone, altered cellular pH in either crypts or the colon cancer cell

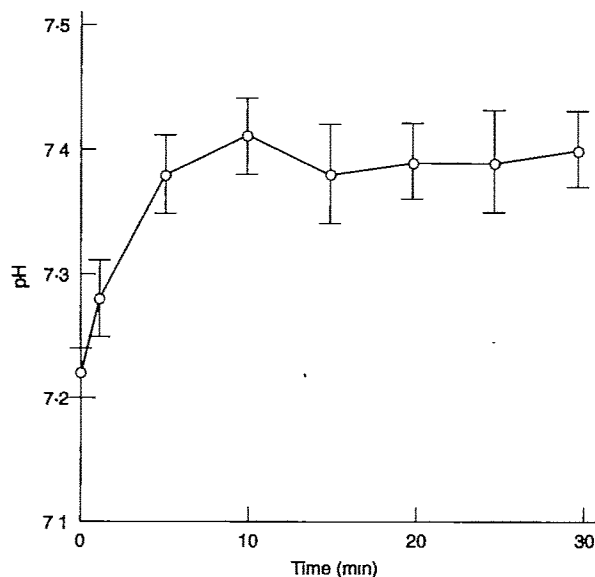


Fig. 1 Effect of 17β -oestradiol on intracellular pH in isolated colonic crypts measured by spectrofluorescence imaging. Oestradiol 1 nmol/l was perfused at time zero and a rapid alkalinization of the cells was observed within minutes. Values are mean(s.e.m.) ($n = 16$)

lines ($n = 8$, $P > 0.6$; 1 pmol/l to 1 μ mol/l for all). Therefore, this steroid hormone action is specific to 17β -oestradiol, the principle naturally produced oestrogen.

Oestradiol-induced alkalinization of crypts was attenuated with 5-(*N*-ethyl-*N*-isopropyl)amiloride (EIPA) 50 μ mol/l, a specific NHE inhibitor²⁹ (maximal pH change 0.02(0.01); $n = 8$, $P < 0.01$). Similarly, the effect of oestradiol on cytoplasmic pH was reduced by EIPA in T84 cells (maximal pH change 0.05(0.02); $n = 8$, $P < 0.01$) and Caco2 cells (maximal pH change 0.02(0.01); $n = 6$, $P < 0.01$). There are limitations to experiments with pharmacological inhibition of the NHE owing to indirect effects. Therefore, the NHE was blocked in separate experiments by removing extracellular sodium (the driving force for activity). Crypts (pH change 0.04(0.01); $n = 6$, $P < 0.001$) and T84 cells (pH change 0.02(0.01); $n = 6$, $P < 0.001$) had little response to oestradiol under these imposed conditions. Caco2 cells did not respond to oestradiol in the absence of extracellular sodium ($n = 6$; $P < 0.001$). This confirms that an increase in NHE activity mediates the rapid-onset, oestradiol-induced alkalinization of human colonic tissue.

The rapidity of the oestradiol action on colonic cells indicated that it was unlikely to be mediated by the classical receptor mechanism (i.e. via gene transcription and protein synthesis). Genomic protein synthesis was abrogated by blockade of DNA transcription and messenger RNA (mRNA) translation, with actinomycin D 20 μ g/ml and cycloheximide 10 μ g/ml respectively, in separate experiments. Under these conditions, oestradiol induced a similarly rapid change in cytoplasmic pH that was indistinguishable from controls in crypts (0.19(0.03); $n = 6$, $P > 0.4$), T84 cells (0.20(0.03); $n = 6$, $P > 0.1$) and Caco2 cells (0.12(0.04); $n = 6$, $P > 0.1$). This confirms that oestradiol activates the NHE by a non-genomic mechanism transduced by membrane or cytoplasmic signals.

Many growth factors stimulate pH changes by protein kinase-mediated phosphorylation of the NHE^{26,27,29}. Direct activation of PKC with a phorbol ester (phorbol 12-myristate-13-acetate 1 μ mol/l) resulted in cellular alkalinization in crypts (pH change 0.25(0.04); $n = 6$, $P < 0.001$) and T84 cells (pH change 0.27(0.06); $n = 6$, $P < 0.001$). This was confirmed as a PKC-mediated event by inactivating the enzyme with chelerythrine chloride 1 μ mol/l (Fig. 2). Phorbol ester-induced alkalinization was inhibited by blocking the NHE with EIPA in crypts (pH change 0.06(0.02); $n = 6$, $P < 0.01$) and T84 cells (pH change 0.09(0.03); $n = 6$, $P < 0.01$). PKC inhibition also blocked the oestrogen-induced activation of the NHE in crypts and T84 cells (Fig. 2). These data indicate that the non-genomic oestradiol action is PKC dependent, and that PKC stimulation alone is a sufficient signal to alter cytoplasmic pH in human colonic cells.

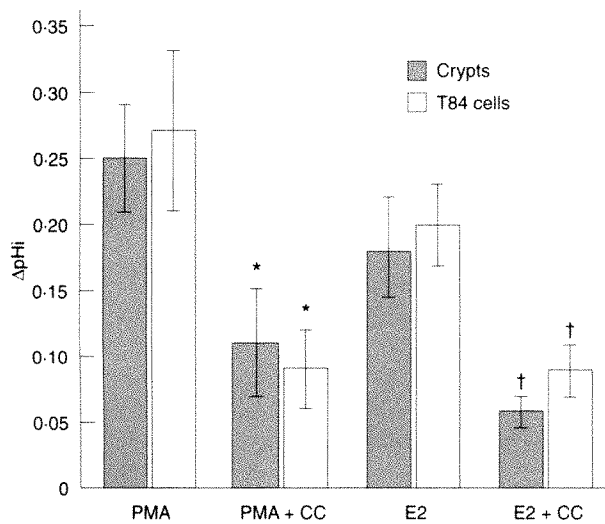


Fig. 2 Role of protein kinase C (PKC) in non-genomic oestrogen action on colonic crypts and cancer cells of human origin. Phorbol ester (PMA)-induced alkalization of both cell types was significantly inhibited by blocking PKC with chelerythrine chloride (CC). Similarly, oestradiol (E2)-mediated alkalization was significantly inhibited by blocking PKC. Values are mean (s.e.m.) changes in intracellular pH (ΔpHi) ($n = 6$). * $P < 0.001$ versus PMA, † $P < 0.01$ versus E2 (Mann-Whitney U test)

The effect of 17β -oestradiol on nuclear kinetics independent of gene-directed influences was explored using [^3H]thymidine incorporation in the presence of the protein synthesis inhibitor cycloheximide. DNA replication activity (measured over 12 h; $n = 6$ in all experiments) was exhibited by crypts (5680.2(167.5) c.p.m.), T84 cells (10158.2(211.8) c.p.m.), Caco2 cells (8431.7(491.3) c.p.m.) and HCT15 cells (11208.7(826.0) c.p.m.). Oestradiol increased DNA replication by 44 per cent in human colonic crypts (8179.5(291.2) c.p.m.; $P < 0.01$) but did not significantly alter HCT15 kinetics ($P > 0.3$) over this time period. Meanwhile, oestradiol increased DNA kinetics by 38 per cent in T84 cells (14024.6(323.1) c.p.m.; $P < 0.01$) and by 25 per cent in Caco2 cells (10571.0(761.1) c.p.m.; $P < 0.05$). The oestrogen antagonist ICI 182 780 inhibited oestradiol stimulation of thymidine uptake in crypts (6353.8(371.4) c.p.m.), T84 cells (12069.1(263.8) c.p.m.) and Caco2 cells (9212.3(214.6) c.p.m.) ($P < 0.01$ versus oestrogen controls in all). The stimulatory effect of oestradiol on DNA replication was reduced by inhibiting the NHE with EIPA in crypts (6305.0(276.1) c.p.m.; $P < 0.01$), T84 cells (10462.9(381.9) c.p.m.; $P < 0.01$) and Caco2 cells (8883.9(720.3) c.p.m.; $P < 0.05$). In separate experiments, in which PKC was blocked with chelerythrine chloride, oestradiol-mediated increases in DNA activity

were also inhibited in crypts (6589.0(214.3) c.p.m.; $P < 0.05$), T84 cells (11478.8(342.7) c.p.m.; $P < 0.05$) and Caco2 cells (8914.4(529.1) c.p.m.; $P < 0.05$). None of the other steroid hormones tested (progesterone, testosterone, 17α -oestradiol and oestrone) influenced nuclear kinetics in crypts or the colon cancer cell lines ($P > 0.3$ for all).

Discussion

The traditional concept of steroid hormone action, in which ligation of a unique receptor within the target cell upregulates gene-directed protein synthesis, remained unchallenged for several decades²⁰. It was recently established that two isoforms of the intracellular oestrogen receptor (denoted alpha and beta) are expressed in most target tissues³⁰. Although one is exclusively in the nucleus and the other in the cytoplasm, both isoforms are characterized by such gene transcription, or genomic, responses³⁰. Membrane binding sites for oestrogen were identified in the endometrium over 20 years ago, but their function was not determined³¹. Similarly, membrane binding sites for oestrogen and other steroids have been found in other tissues^{32–35}. Amid these findings, there is an emerging concept that faster effects of oestrogen exist which involve a membrane-associated signalling distinct from genomic influence²¹. In this study, rapidly responsive, non-genomic effects of oestrogen were demonstrated in normal and malignant colonic tissue of human origin.

The endogenously produced oestrogen, 17β -oestradiol, induced an alkalization of colonic crypts and colon cancer cells at physiological concentrations. The rapidity of this response and the inability to block it with inhibitors of DNA transcription and mRNA translation is in keeping with a non-genomic steroid hormone action. Similar effects of the mineralocorticoid aldosterone were described recently in colonic crypts²². Steroid hormones with structural similarity to oestradiol were assessed for non-genomic effects (progesterone, 17α -oestradiol and oestrone). The rapid change in pH was seen only with 17β -oestradiol, suggesting that two hydroxyl groups are required for this receptor coupling. This underlines the potentially different effects of natural oestrogens and hormone replacement therapy on the colon^{7–10}. Moreover, the lack of response to testosterone suggests that sex differences in the behaviour of normal and malignant colonic cells exist.

The cellular alkalization was demonstrated to be mediated by extrusion of protons from the cells by exchange with sodium ions. These exchangers (NHEs) reside on the plasma membrane and are activated by a variety of stimuli^{26,27,29}. Several isoforms exist but the profile of the oestrogen-sensitive subtype outlined in this study (i.e. present in crypts and blocked by EIPA) is consistent with

NHE1²⁹. This isoform is expressed ubiquitously in the body and is the key regulator of intracellular pH²⁹. Since it is regulated by protein kinases NHE1 plays a role in the action of hormones, neurotransmitters and pharmacological agents. For example, dopamine inhibits renal and colonic NHE1 via protein kinase A, resulting in diuresis and intramucosal acidification respectively³⁶. The calcium-dependent protein kinase (PKC) is generally stimulatory to NHE1 and may be rapidly activated by steroid hormones^{23–27,29}. Therefore, the role of PKC in the non-genomic oestrogen action was explored in this study. It was found that oestrogen-induced upregulation of NHE1 in colonic crypts and cancer cells was significantly reduced by inhibiting PKC. Furthermore, direct activation of PKC with a phorbol ester mimicked the effect of oestrogen on the cells. These data provide strong evidence that NHE1 activity is increased by a PKC-mediated pathway in this non-genomic oestrogen mechanism.

The growth stimulatory potential of PKC-related NHE activation has been described in several epithelial and haematogenous cells²⁶. Such mitogenic influences are due primarily to enhanced DNA replication activity. The intimate relationship between NHE-induced alkalinization and nuclear kinetics prompted the investigation of a potential mitogenic stimulus by oestrogen in this study. In order to abrogate the influence of gene-directed protein synthesis (i.e. genomic effects) in these experiments, crypts and colon cancer cells were exposed to a protein synthesis inhibitor as described previously^{22,23}. Despite this restriction, both cell types responded to oestrogen with an increase in DNA replication activity that was inhibited by blockade of either NHE1 or PKC. These results confirm that oestrogen mediates a mitogenic influence on both normal and cancerous cells of human colonic origin in a previously unrecognized, non-genomic fashion.

Tamoxifen, a weak oestrogen antagonist, exhibits modest growth inhibitory activity in colorectal cancer cell lines, including those lacking intracellular, genomic receptor expression^{18,19}. This is not surprising because tamoxifen perturbs cell signalling cascades required for function and growth independent of oestrogen receptor coupling^{37,38}. However, rapidly responsive, non-genomic effects of oestrogen on cellular ion transport are not inhibited significantly by tamoxifen²¹. In the present study, a more potent and specific antioestrogen compound blocked the non-genomic action of oestrogen on cell membrane kinetics. Meanwhile, oestrogen did not evoke a membrane response in cancer cells that do not possess classical oestrogen receptors. Therefore, the non-genomic mechanism of oestrogen is mediated by binding sites that share some homology with the classical, intracellular receptors, yet display spatial and functional segregation suggesting a

cell membrane domain. Furthermore, the insensitivity of the non-genomic action to tamoxifen (in contrast to the classical, genomic action) may explain the variable and sometimes disappointing responses to this drug as an antioestrogen in laboratory and clinical settings^{18,19,21,24,25,37}.

Epidemiological and molecular data have provided impressive evidence that oestrogen plays a role in the genesis and perpetuation of colorectal cancer^{2–10}. Oestrogen stimulates colon cancer growth, and physiological or pharmacological antioestrogen therapy retards large bowel tumours^{11,17–19}. The mechanism by which oestrogen exerts this proliferative influence has been assumed to be at the oncogene, transcription or translational level, in keeping with a proposed genomic transduction. Therefore, the present finding that oestrogen exerts a mitogenic stimulus via a non-genomic mechanism, independent of gene-directed protein synthesis, is of relevance to the pathobiology of large bowel cancer. Furthermore, the non-genomic signal transduction pathway and the putative membrane receptor represent potential targets for inhibiting colorectal cancer growth in the clinical setting. For example, the tumoricidal properties of compounds that disrupt cellular pH regulation, including NHE blockade in colon cancer, have been reported³⁹. Moreover, since it is mediated by a ubiquitous signalling axis, the therapeutic implications of this distinct oestrogen action are not limited to the colon. Oestrogenic stimulation of a 50-kDa protein regulator of the NHE was described recently in mammary tissue⁴⁰. The implications of a mitogenic response to oestrogen in a novel, non-genomic fashion formulate an exciting area for further evaluation in breast and bowel cancer.

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Hyaluronic acid as prognostic marker in resectable colorectal cancer

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Background: Hyaluronic acid (HA), an extracellular high molecular mass polysaccharide, is thought to be involved in the growth and progression of malignant tumours. The objective of this work was to evaluate the cytosolic HA content in resectable colorectal cancer, its possible relationship with clinicopathological parameters of tumours and its prognostic significance.

Methods: Cytosolic HA levels were examined by radiometric assay in 120 patients with resectable colorectal cancer. The mean follow-up period was 33.4 months.

Results: Cytosolic HA levels of tumours ranged widely, from 30 to 29 412 ng per mg protein. Intratumour HA levels were significantly correlated with Dukes stage ($P < 0.005$), and were higher in patients with advanced tumours (mean(s.e.m.) 2695(446), 2858(293) and 5274(967) ng per mg protein for stages A, B and C respectively). In addition, Cox multivariate analysis demonstrated that tumour HA levels higher than 2000 ng per mg protein predicted shorter relapse-free survival and overall survival periods (both $P < 0.05$).

Conclusions: There is a wide variability in cytosolic HA levels in colorectal carcinomas, which seems to be related to the biological heterogeneity of these tumours. In addition, high tumour cytosolic HA levels were associated with an unfavourable outcome in patients with resectable colorectal cancer. HA may provide additional information to that given by other biochemical markers currently used in colorectal cancer.

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Introduction

Hyaluronic acid (HA), also known as hyaluronan or hyaluronate, is a widespread polysaccharide which is found on the cell surface and in the extracellular matrix of almost every human tissue^{1,2}. HA differs from other glycosaminoglycans in that it is considerably larger, having a molecular mass of up to 1×10^7 Da. It is synthesized in the plasma membrane by the enzyme HA synthase and is extruded while still elongating into the extracellular matrix³. Raised concentrations of HA are normally associated with the physiological tissue remodelling process characterized by rapid cellular proliferation, as in healing wounds and during foetal development^{2,4}. Nevertheless, raised concentrations of HA have also been found in several human tumours such as mesothelioma⁵, Wilms' tumour⁶, breast⁷, gastric^{8,9} or

colorectal^{10,11} carcinomas. In addition, in neoplastic tissues, increased concentrations of HA stimulate cell motility¹², cell adhesion¹³ and neovascularization¹⁴. Furthermore, cells bind to HA through at least two cell surface receptor proteins, CD44 and RHAMM¹⁵. The interaction between CD44 and its main ligand HA is presumed to be associated with invasive potential¹⁵. It has also been demonstrated that cancer cells covered by an HA coat may be protected from cytotoxic cells¹⁶ or chemotherapeutic agents^{17–19}.

In accordance with these latter findings that point to a putative role of HA in tumour progression, recent clinical reports have indicated a relationship between tumour HA expression and a poor outcome in patients with gastric⁹ or colorectal cancer¹¹. This study examined tumour HA content in a large series of patients with resectable colorectal cancer, its possible relationship with clinicopathological parameters and its prognostic significance. The results showed a significant and positive correlation between intratumoral HA levels and tumour stage. In

The Editors have satisfied themselves that all authors have contributed significantly to this publication

Table 1 Cytosolic hyaluronic acid levels in resectable colorectal carcinomas: correlation with clinicopathological parameters

	No. of patients	HA (ng per mg protein)		P
		Mean(s.e.m.)	Median (range)	
All patients	120	3540(346)	2462 (30–29 412)	
Age (years)				
< 65	34	3710(542)	2600 (30–15 088)	}
> 65	86	3472(434)	2340 (185–29 412)	
Sex				
Male	53	3163(378)	2216 (30–15 088)	}
Female	67	3837(542)	2765 (304–29 412)	
Tumour location				
Right	40	2881(327)	2164 (788–10 798)	}
Transverse	6	3518(1299)	3014 (30–8441)	
Left	44	4061(752)	2544 (304–29 412)	
Rectum	30	3657(670)	2790 (185–17 026)	
Stage				
A	17	2695(446)	2198 (304–7825)	}
B	68	2858(293)	2064 (30–14 148)	
C	35	5274(967)	3769 (451–29 412)	
Histological grade				
Well differentiated	28	3148(662)	1969 (30–17 026)	}
Moderately differentiated	84	3459(313)	2790 (185–15 088)	
Poorly differentiated	8	5760(3408)	2234 (827–29 412)	
DNA ploidy status				
Diploid	48	3094(388)	2204 (185–14 148)	}
Aneuploid	43	4304(800)	5304 (415–29 412)	
Unknown	29	3016(1717)	2571 (30–6693)	
S-phase fraction				
Low (< 13.7%)	45	4140(699)	3114 (415–29 412)	}
High (> 13.7%)	46	2900(455)	1944 (185–15 088)	

All patients were without signs of distant metastases at the time of surgery. HA, hyaluronic acid; n.s., not significant

addition, high HA levels in tumours were significantly and independently associated with a poor outcome after colorectal cancer resection.

Patients and methods

Patient characteristics and tissue specimen handling

Samples of colorectal carcinoma were obtained from 120 consecutive patients with resectable colorectal cancer (R₀, according to recommendations of the Union Internacional Contra la Cancrum)²⁰. Adjacent mucosa samples were also obtained from 77 of these patients. Biological and clinical features of the patients are listed in *Table 1*. Tumours were staged according to Dukes²¹ and Broders²² classifications. The mean follow-up period was 33.4 (range 12–69) months. Adjuvant therapy with 5-fluorouracil and levamisole was given to patients with Dukes C tumours, and locoregional radiotherapy was also given to those with rectal tumours. Thirty of 120 patients developed tumour recurrence (20 with distant metastases, four with local recurrence and six

with both types of tumour recurrence), of whom 26 died from recurrence.

Samples were removed from the tumours, avoiding grossly necrotic tissues, and a region of surrounding mucosa at least 2 cm from the tumours. The mucosa surrounding the neoplasms was found to be macroscopically and microscopically free from neoplastic growth. Immediately after surgical resection, samples were processed for pathological examination while the remainder were washed with cold saline solution, divided into aliquots, rapidly transported on ice to the laboratory, and stored at –70°C pending biochemical and cytochemical studies.

Flow cytometric DNA analysis

DNA content was evaluated in 91 tumours by flow cytometry (Becton Dickinson, San José, California, USA) on nuclei obtained from tissues and stained with propidium iodide. DNA ploidy was expressed as DNA index. Proliferative activity was expressed as the fraction of cells

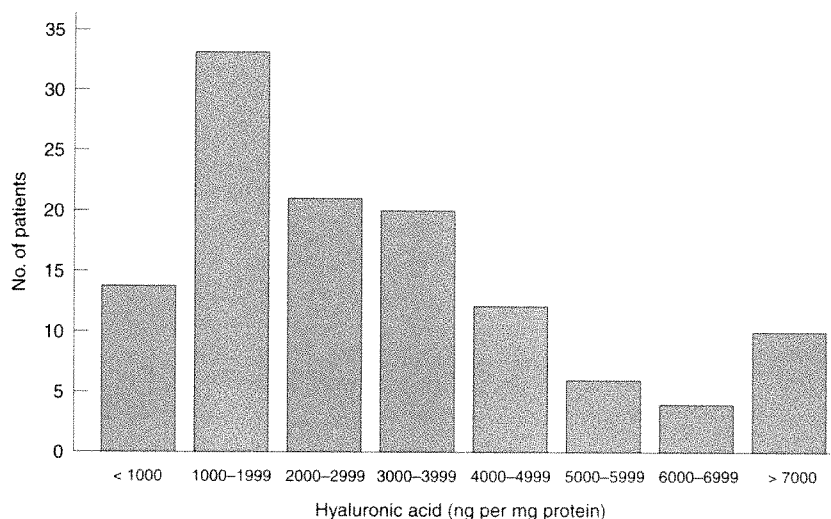


Fig. 1 Distribution of cytosolic hyaluronic acid levels in 120 colorectal carcinomas

in the S phase of the cell cycle and calculated according to the recommendations of the DNA Cytometry Consensus Conference²³ with the CellFit software program (Becton Dickinson). Median S-phase fraction value was used as the cut-off point. Tumours were divided into those with a high or low S-phase fraction.

Tissue processing and hyaluronic acid assay

Specimens from neoplastic and normal surrounding tissues were processed at the same time. They were pulverized with a microdismembrator (Braun, Melsungen, Germany) at -70°C and homogenized in Tris hydrochloride (Tris 10 mmol/l, ethylenediamine tetra-acetic acid 1.5 mmol/l, 10 per cent glycerol, 0.1 per cent of monothioglycerol) pH 7.4. Homogenates were centrifuged at 800g for 10 min at 4°C , and supernatant was ultracentrifuged at 10 000g for 60 min at 4°C . HA was measured in cytosolic samples using a commercially available protein binding radio assay (Pharmacia, Uppsala, Sweden), based on the use of specific HA-binding proteins, previously isolated from bovine cartilage. The sensitivity of the method was 1 ng/ml. The intra-assay coefficients of variation at 29.0 and 85.9 ng/ml were 6.5 and 4.5 per cent respectively; the interassay coefficients of variation at the same concentrations were 4.9 and 8.5 per cent respectively. Protein content was quantified by the Bradford method²⁴.

Statistical analysis

Tumour cytosolic HA content was expressed as mean (s.e.m.). The differences in HA content between tumour

tissues and paired normal mucosa samples were compared using Wilcoxon's signed rank test. Patients were subdivided into groups based on different clinical and pathological parameters. Comparison of the HA content between groups was made with Mann-Whitney and Kruskal-Wallis tests. Probabilities of relapse-free and overall survival were calculated with the Kaplan-Meier method²⁵. Differences between curves were evaluated with the log rank test²⁶. Cox's regression model²⁷ was also used to examine several combinations and interactions of prognostic factors in a multivariate analysis. The following variables were included in the analysis: location, histological grade and stage of tumours. Prognostic variable selection was performed with Cox's model using the stepwise regression option from BMDP (program 2L) software²⁸ (BMDP, Los Angeles, California, USA). The *P* value at which covariables were entered or removed was 5 per cent. Differences were considered significant at $P < 0.05$.

Results

There was a wide variability of cytosolic levels of HA in neoplastic tissue (30–29 412 ng per mg protein) and in samples of adjacent mucosa (49–5927 ng per mg protein). There were no significant differences between neoplastic and paired adjacent mucosa samples ($n = 77$; 3294(442) versus 3076(167) ng per mg protein). The distribution of cytosolic HA levels in 120 tumours is shown in Fig. 1. Table 1 shows the distribution of cytosolic HA levels in relation to patient and tumour characteristics including age, sex, tumour location, Dukes stage, histological grade, DNA ploidy and S-phase fraction. Statistical analysis showed that HA levels were

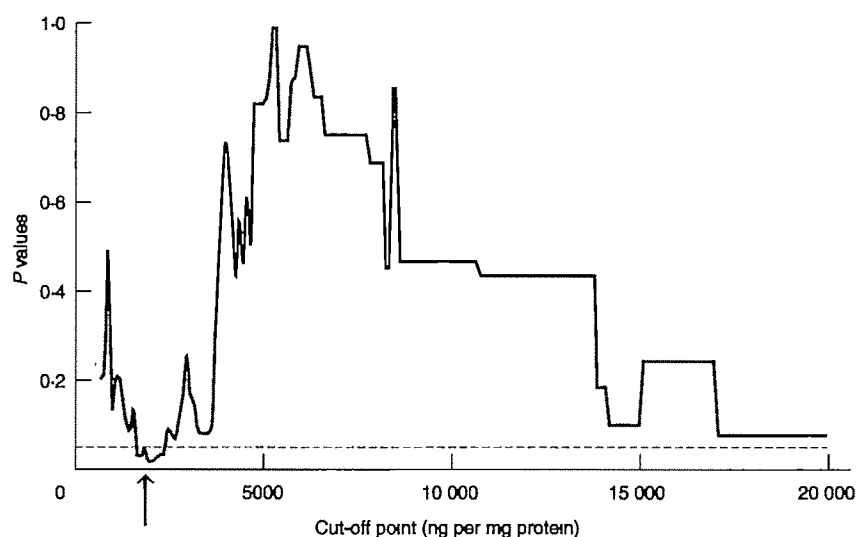


Fig. 2 Maximal likelihood determination of the cut-off value of hyaluronic acid (HA) cytosolic content in neoplastic tissues for predicting relapse-free survival in 120 patients with resectable colorectal cancer. *P* values obtained for each cut-off value are plotted against the value itself. Statistical significance is indicated by the dotted line at the 0.05 level. A cytosolic HA level of 2000 ng per mg protein (arrow) was defined as the optimal cut-off ($\chi^2 = 4.68$, d.f. = 1, $P = 0.03$)

significantly correlated with clinical tumour stage ($P < 0.005$); HA levels were higher in patients with more advanced tumours (2695(446), 2858(293) and 5274(967) ng per mg protein for stage A, B, and C respectively). However, there was no correlation between tumour HA content and age, sex, tumour location, histological grade, DNA content or S-phase fraction (Table 1).

The potential association between cytosolic HA levels of tumours and relapse-free and overall survival was evaluated prospectively in the 120 patients. First, an optimal cut-off value was defined by statistical analysis of the ability of cytosolic HA values to predict the relapse-free survival of the study population. This statistical analysis showed a continuous association between a cytosolic HA concentration of 1700 and 2400 ng per mg protein and relapse rate ($P < 0.05$). Further analysis led to the definition of a cytosolic HA content of 2000 ng per mg protein as the optimal cut-off ($\chi^2 = 4.68$, d.f. = 1, $P = 0.03$), with ability to identify 61 per cent of patients as having tumours with a high cytosolic HA content (Fig. 2). Considering this cut-off value, relapse was confirmed in 23 (32 per cent) of 73 patients with tumours containing high cytosolic HA levels, but in only seven (15 per cent) of 47 with tumours showing low HA levels. There were 20 deaths (27 per cent) from recurrence in patients with tumours showing high cytosolic HA levels and only six deaths (13 per cent) in patients whose tumours had a low HA content. Differences between both recurrence-free survival and overall survival curves were significant ($P = 0.02$ and $P = 0.03$ respectively) (Fig. 3).

Multivariate analysis according to Cox's model confirmed that cytosolic HA content was significantly associated with relapse-free and overall survival in this group of patients with resectable colorectal cancer ($P < 0.05$ for both) (Table 2).

Discussion

This is, to the authors' knowledge, the first clinical study of HA content in colorectal cancer using a radiometric assay. There was a wide variability in cytosolic HA levels in colorectal carcinomas, which seems to correspond to the biological heterogeneity of these tumours. In addition, there was a significant and positive correlation between tumour HA level and tumour stage. Nevertheless, high cytosolic HA levels were significantly and independently associated with both short relapse-free and overall survival times in patients with resectable colorectal cancer.

The stroma of the majority of malignant tumours, including colorectal cancer, has been shown to contain more HA than the corresponding normal tissues^{10,29}. However, the present study did not show significant differences in HA cytosolic content between tumours and adjacent mucosa samples. Although little is known about the expression of HA in cancer cells, immunohistochemical analysis has demonstrated that some colorectal tumours contain unusual apical intracellular HA staining in the cancer cells^{10,11}. The present finding of high cytosolic HA levels in a significant percentage of colorectal carcinomas

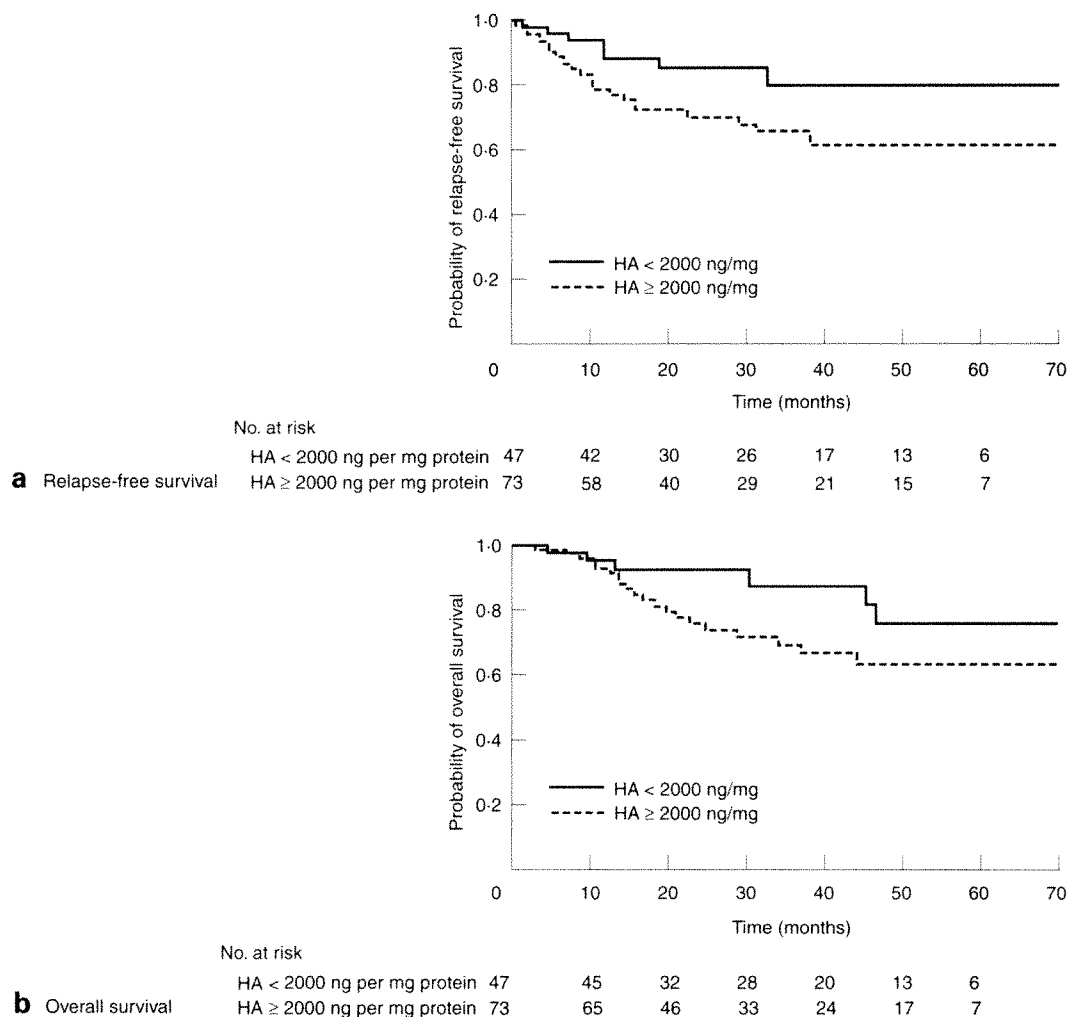


Fig. 3 **a** Relapse-free and **b** overall survival as function of cytosolic hyaluronic acid (HA) level in neoplastic tissues in 120 patients with resectable colorectal carcinoma. The cut-off point was defined as 2000 ng per mg protein. Mean follow-up was 33.4 months. $P = 0.02$ for relapse-free survival, $P = 0.03$ for overall survival (log rank test)

Table 2 Multivariate analysis of association of cytosolic hyaluronic acid levels in tumours with relapse-free and overall survival in 120 patients with resectable colorectal cancer

	Relapse-free survival			Overall survival		
	Relative risk		<i>P</i>	Relative risk		<i>P</i>
Dukes stage						
A	0.25	}	0.0017	0.19	}	0.0007
B	0.68			0.65		
C	1.85			2.17		
Histological grade						
Well differentiated	—	}	0.0317	0.43	}	0.0471
Moderately differentiated	—			1.00		
Poorly differentiated	—			2.31		
HA (ng per mg protein)						
< 2000	0.62	}	0.0317	0.62	}	0.0489
≥ 2000	1.53			1.52		

HA, hyaluronic acid

might be in accordance with these immunohistochemical observations. Several mechanisms have been proposed to explain the accumulation of HA within a malignant tumour. The intracellular signal of HA in cancer cells may be related to CD44, which has been shown to mediate uptake of HA in other cell types^{30–32}. CD44 is the predominant HA cell surface receptor protein^{12,33}, and is upregulated in colon cancers. Moreover, exon-v6-containing CD44, one of its high molecular weight variants, is associated with poor overall survival in colon cancer^{34,35}. However, the presence of CD44 does not exclude activation of HA synthase, since cell surface HA may remain bound to HA synthase³⁶. This may mean that CD44 is not required for the expression of HA at the cell surface, and that other unknown mechanisms may be implicated in the origin of HA associated with cancer cells.

It has also been suggested that, in advanced malignancies, raised levels of HA may be the consequence of blockage of lymphatic drainage, which is the route of clearance of tissue HA¹¹. This is in agreement with the present study which showed significantly higher intratumoral HA levels in Dukes C tumours than in Dukes A or B lesions. High tumour HA levels were also significantly and independently associated with tumours of unfavourable prognosis, in accordance with the immunohistochemical findings of Ropponen *et al.*¹¹, who noted that HA intensity in tumour epithelium independently predicted both shortened relapse-free survival and overall survival times in patients with colorectal cancer. These clinical findings suggest that raised HA levels may play a role in tumour growth and spread in colorectal cancer without any association with tumour stage. HA synthesis should be regulated by surrounding stromal fibroblasts opening gaps through connective tissue and thus facilitating cancer cell dissemination²⁹. In addition, it has also been demonstrated that increased concentrations of HA stimulate cancer cell motility¹². Another mechanism of HA involvement is in angiogenesis; HA has different roles in neovascularization depending on its low molecular weight fragments¹⁴, which may be generated by hyaluronidase activity from human colon carcinomas³⁷.

There are other biological aspects of HA that support the clinical results of the present work, indicating a poor outcome for patients with high tumour HA levels. HA may dampen recruitment of cytotoxic lymphocytes¹⁶. It may also protect cancer cells against cytotoxic agents such as doxorubicin, adriamycin and mitomycin C^{17–19}. It has been suggested that the measurement of tumour HA may be useful for the identification of a subgroup of patients whose tumours may be chemoresistant.

In summary, the present results suggest that high tumour HA levels may be associated with unfavourable

prognosis in resectable colorectal cancer. Nevertheless, these are preliminary data and further studies involving larger populations of patients are required to establish the potential value of HA as a new prognostic factor to predict the clinical outcome in patients with colorectal cancer.

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Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease

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Background: Previous studies on risk factors for resection and postoperative recurrence in Crohn's disease have given inconclusive results. The aim of this study was to assess the risk for resection and postoperative recurrence in the treatment of ileocaecal Crohn's disease and to define factors affecting the course of the disease.

Methods: A population-based cohort of 907 patients with primary ileocaecal Crohn's disease was reviewed retrospectively.

Results: Resection rates were 61, 77 and 83 per cent at 1, 5 and 10 years respectively after the diagnosis. Relapse rates were 28 and 36 per cent 5 and 10 years after the first resection. A younger age at diagnosis resulted in a low resection rate. The presence of perianal Crohn's disease and long resection segments increased the incidence of recurrence, and resection for a palpable mass and/or abscess decreased the recurrence rate. A decrease in recurrence rate during the study period (1955–1989) was observed.

Conclusion: In ileocaecal Crohn's disease the probability of resection is high and the risk of recurrence moderate. Crohn's disease in childhood carries a lower risk of primary resection. Perianal disease and extensive ileal resection increase the risk of recurrence.

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Introduction

The clinical course of Crohn's disease is difficult to predict. Some patients experience a low morbidity whereas others need repeated operations. The overall aim of surgery is to reduce symptoms and preserve bowel function. Ileocaecal disease may be controlled with new pharmacological compounds. The main issue is, therefore, to distinguish patients with a high risk of recurrent disease who may benefit more from medical treatment from those who may benefit more from surgery.

Previous studies on risk factors for resection as well as postoperative recurrence in patients with Crohn's disease have given largely inconclusive results. This may be attributable to the small numbers of patients evaluated, different study designs with reference to the types of patient included, type of primary involvement, evaluation of primary resection or reoperation, or a combination of factors. Moreover, the definition of recurrent disease and the length of follow-up has differed¹. Therefore, prediction of outcome following resection in patients with Crohn's disease remains an issue and, in the case of recurrent disease,

the adverse effects of smoking and the presence of perianal disease seem to be the only risk factors agreed upon so far². Hence, there is still a need to define factors that might influence the course of the disease, and further evaluation of patients with Crohn's disease is desirable.

The aims of the present study were to assess the risk and timing of first intestinal resection and postoperative recurrence in a large cohort of patients with primary ileocaecal Crohn's disease, and to define possible prognostic factors that might facilitate the selection of patients for preoperative and postoperative pharmacological treatment.

Patients and methods

The study was based on a subgroup of 907 patients with ileocaecal Crohn's disease who were extracted from a retrospectively assembled cohort of 1936 patients diagnosed with Crohn's disease between 1955 and 1989 in Stockholm County. The study was approved by the local ethics committee.

Details were described previously in an epidemiological study by Lapidus *et al.*³. The diagnosis was established

according to the criteria proposed by Lennard-Jones⁴, including clinical history, radiological and endoscopic examination, macroscopic findings at operation, and histopathological findings. Diagnostic procedures were consistent throughout the study period, except for the gradual introduction of ileocolonoscopy during the 1970s.

Data management and definitions

Case records were scrutinized retrospectively and variables of interest for the study were transferred to a data file (File Maker Pro; Claris, Santa Clara, California, USA). To achieve completeness, data were collected until 1995, finally giving a 99 per cent follow-up rate. Disease localization was established at the time of diagnosis and included patients with inflammation in the distal 30 cm of the ileum, with or without involvement of the caecum. Age at diagnosis was grouped into 15-year intervals except for patients aged more than 60 years at diagnosis, who constituted a single group. Concomitant perianal disease included fissures, abscesses and fistulas in the perianal area, anal canal or rectum at any time during the course of the disease. Indications for surgery included acute abdominal pain, failure of medical therapy, intestinal obstruction, a palpable mass or abscess, internal fistulas or 'other reasons'. Surgery included ileocaecal resection or right hemicolectomy; other types of resection or surgical procedures were excluded. Postoperative complications that led to reoperation were recorded, as was the presence of granuloma on histological examination.

Postoperative recurrence was recorded when patients presented with bowel symptoms consistent with, and later verified as, recurrent Crohn's disease.

Statistical analysis

Probabilities of resection and time trends for recurrence were analysed with the Kaplan-Meier method⁵. The influence of independent variables on the cumulative probability of surgery and recurrence was examined with the proportional hazard model⁶. Probability values and confidence intervals (c.i.) were calculated at the 95 per cent level.

Results

Surgery for ileocaecal Crohn's disease

Eighty-seven per cent (787 of 907) of the patients were eventually treated by primary resection at a median age of 32.1 (range 10–85) and 32.5 (range 9–80) years for males and females respectively. Ileocaecal resection was per-

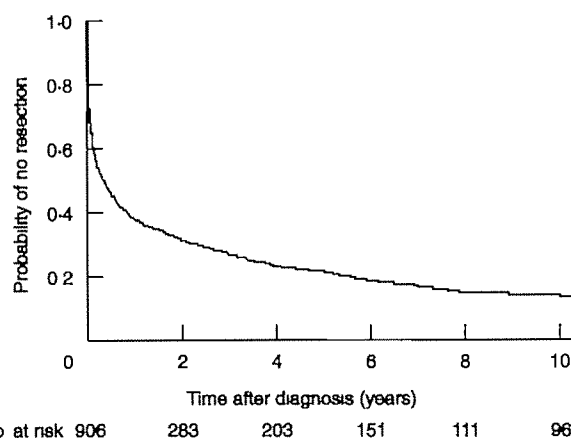


Fig. 1 Kaplan-Meier curve showing the cumulative resection rate during first 10 years after diagnosis of Crohn's disease

formed in 69 per cent (544 of 787) of patients, and 23 per cent (178 of 787) had a right hemicolectomy; 65 patients who underwent other forms of resection were excluded from the analysis. The resection was performed at a median of 1.6 (range 0–264) and 2.9 (range 0–216) months after diagnosis in the ileocaecal resection and right hemicolectomy groups respectively. The cumulative frequency of resection was 61 (95 per cent c.i. 59–64), 77 (75–79) and 83 (82–84) per cent 1, 5 and 10 years respectively after diagnosis (Fig. 1).

Postsurgical complications occurred in 9 per cent of patients following ileocaecal resection and in 7 per cent after right hemicolectomy. The most common complication was anastomotic leakage or abscess formation (3 per cent). Postoperative death occurred in seven patients (1 per cent) as a result of anastomotic dehiscence (four patients), bleeding (one), heart failure (one) and cerebral haemorrhage (one).

A trend towards more frequent use of ileocaecal resection instead of right hemicolectomy throughout the study period was seen (Fig. 2). Possible factors that influenced the probability of resection are shown in Table 1. The only significant factor was that patients of a younger age (0–14 years) at diagnosis had a decreased relative risk (RR) of resection: 0.7 (95 per cent c.i. 0.5–0.9). Gender did not affect the probability of surgery, nor did the presence of perianal disease. Furthermore, no particular trend in resection rates was demonstrated on comparing the study period of 1955–1974 with that of 1975–1989 ($P=0.25$).

Postoperative recurrence

Forty-three per cent (307 of 722) of the patients who had undergone primary resection eventually had a symptomatic

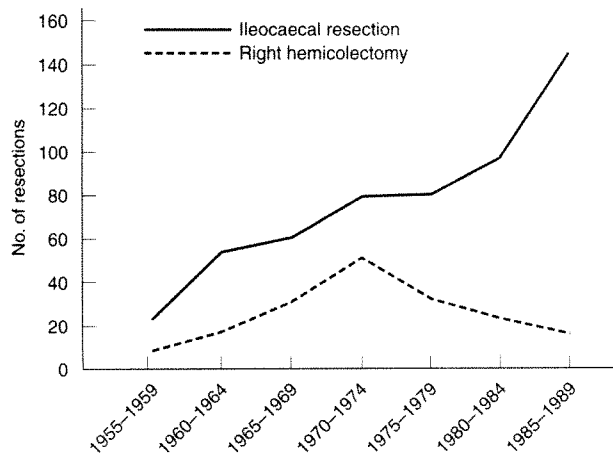


Fig. 2 Curves showing the trend towards ileocaecal resection as the primary surgical procedure in patients with ileocaecal Crohn's disease between 1955 and 1989

Table 1 Multivariate analysis of risk factors for first intestinal resection in 873 patients diagnosed with ileocaecal Crohn's disease

	No. of patients	P†	Relative risk
Age at diagnosis (years)			
0-14	59	0.01	0.7 (0.5-0.9)
15-29*	368		1.0 (alive)
30-44	228	0.93	1.0 (0.8-1.2)
45-59	143	0.19	1.1 (0.9-1.4)
60 or more	75	0.47	1.0 (0.8-1.5)
Female sex		0.53	1.0 (0.8-1.1)
Perianal fistula		0.27	1.0 (0.9-1.3)

Values in parentheses are 95 per cent confidence intervals. *Reference group. †Multivariate value

relapse after a median of 6.8 years. The cumulative rate was 28 (95 per cent c.i. 25-30) and 36 (33-37) per cent after 5 and 10 years respectively. Factors of possible prognostic value in recurrence were evaluated in 476 patients (Table 2). A history of perianal disease and resection of long segments (more than 50 cm) of the distal ileum increased the risk of relapse with a RR of 1.6 (95 per cent c.i. 1.2-2.3) and 1.4 (1.0-1.8) respectively, whereas patients who had surgery for a 'palpable mass or abscess' had a decreased risk, with a RR of 0.5 (95 per cent 0.2-0.9). Moreover, patients diagnosed during 1975-1989 had a significantly lower cumulative relapse rate than those diagnosed during 1955-1974 ($P=0.03$) (Fig. 3). No impact of gender, age at diagnosis, preoperative duration of disease, type of resection, post-operative complications or presence of granuloma was found.

Table 2 Multivariate analysis of risk factors for recurrent disease in 476 patients who had primary resection for ileocaecal Crohn's disease

	No. of patients	P†	Relative risk
Perianal fistula			
Yes	114	0.003	1.6 (1.2-2.3)
No*	362		1.0
Indication for first resection			
Acute abdominal pain	46	0.23	0.7 (0.3-1.3)
Medical therapy failure	33	0.68	1.1 (0.6-2.0)
Internal fistula	31	0.67	1.0 (0.6-2.0)
Palpable mass or abscess	42	0.04	0.5 (0.2-0.9)
Other	4	0.99	1.0 (0.3-4.2)
Obstruction*	320		1.0
Length of resection			
Long	226	0.05	1.4 (1.0-1.8)
Short*	250		1.0
Female sex		0.32	1.2 (0.8-1.2)
Age group at diagnosis (four groups)		0.84	—
Duration of disease <2 years		0.66	0.9 (0.7-1.3)
Elective resection		0.53	0.9 (0.5-1.4)
First ileocaecal resection		0.84	1.0 (0.7-1.3)

Values in parentheses are 95 per cent confidence intervals. *Reference group. †Multivariate value

Discussion

This study focused on a defined group of patients with ileocaecal Crohn's disease in a geographically well defined area over a long period of time and with a high rate of follow-up. Bias, which usually hampers hospital series with small numbers of patients and referrals, should therefore have been avoided. The results confirm that Crohn's disease localized to the ileocolonic junction carries a high risk of early surgical resection⁷. The 87 per cent crude rate of at least one intestinal resection found in this study was close to the 91.5 per cent probability of undergoing operation reported by Farmer *et al.*⁸. These values may, however, reflect the Cleveland Clinic's function as a tertiary referral centre for inflammatory bowel disease. Lower resection rates of 51 per cent have been reported from New York⁹, and 40 per cent from Ireland¹⁰, although the latter study included only 19 patients with ileocaecal Crohn's disease.

In this study the majority of patients (61 per cent) had a resection within the first year of the diagnosis, indicating a high morbidity rate during the initial phase of ileocaecal Crohn's disease. This is probably best explained by the fact that approximately half the patients had obstructing or fibrostenotic symptoms that demanded surgical intervention. The cumulative probability of surgery levelled off over time, although 83 per cent of patients with ileocaecal Crohn's disease required at least one intestinal resection

during their lifetime. The low surgical resection rate among children found in the present study was confirmed by another study from Stockholm¹¹ and may be the result of a more conservative attitude towards resection in this age group.

Increased recurrence rates in ileocaecal Crohn's disease compared with small bowel and colorectal disease have recently been demonstrated¹² and, previously, rates of 29–52 per cent were reported^{13,14}. However, regardless of primary disease localization, most studies have evaluated all patients together^{15–19} (Table 3). The varying results in different series are probably due to the use of imprecise definitions of recurrence and different duration of follow-up. The 43 per cent 10-year rate of symptomatic recurrence found in the present study should be reliable.

In this study the presence of perianal fistula and resection of long distal ileum segments increased the risk of postoperative recurrence, whereas resection for a palpable

mass or abscess resulted in a decreased recurrence rate. It is reasonable to assume that patients with concomitant perianal disease constitute a subgroup that has a more severe course of disease. Evaluating recurrence in relation to the indication for operation entails difficulties, as surgery is frequently performed for more than one indication in patients with Crohn's disease. It therefore remains unclear whether the low relapse rate found after resection for a palpable mass and/or abscess in the present study is relevant. Perforating indications such as fistula or abscess, often with advanced inflammation as the main characteristic, are thought by some investigators to be associated with a more aggressive, frequently relapsing strain of Crohn's disease²⁰. This view is not supported by the present study, nor by other evaluations^{2,21}. Moreover, it is likely that extensive primary resections were associated with more widespread disease of the terminal ileum, which may be more inclined to recur. However, bias could be caused by the trend from radical towards limited resection, as was evident in the present study. Furthermore, the shift from right hemicolectomy, which was largely preferred in the 1950s and 1960s as a means of providing wide resection margins on the colonic side of the anastomosis, to a more frequent use of ileocaecal resection occurred without increased relapse rates. Theoretically, this gradual decrease in recurrence may reflect a bias from postoperative pharmacological treatment not accounted for in this study. However, azathioprine was used only rarely at this time, especially in ileocaecal Crohn's disease, and neither 5-aminosalicylic acid compounds nor budesonide were introduced in Sweden before the 1990s.

The impact of the presence of granulomas in resected specimens on recurrence rates remains uncertain^{22,23}. The present study supports the view that the presence of granulomas does not influence the postoperative disease course. Similarly factors such as sex, age at onset, duration of the disease and whether emergency or elective resection was undertaken did not influence the course of the disease.

In conclusion, in the present evaluation of ileocaecal Crohn's disease, the likelihood of operation, risk of recurrence and independent risk factors were clarified.

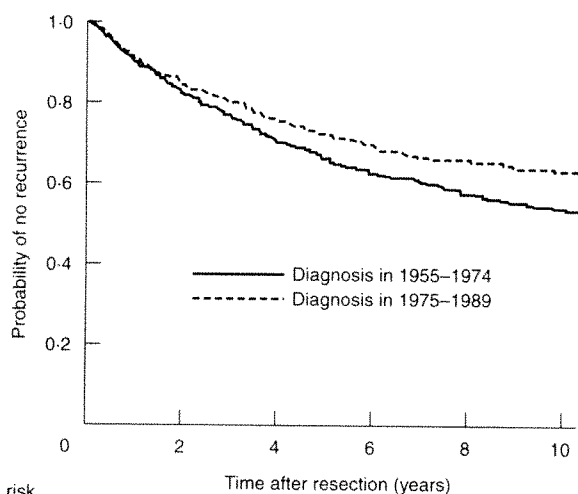


Fig. 3 Kaplan-Meier curves showing cumulative recurrence in patients with an early diagnosis (1955–1974) ($n = 356$) versus a later diagnosis (1975–1989) ($n = 362$). $\chi^2 = 4.7$, 1 d.f., $P = 0.03$

Table 3 Recurrence rates in previous studies of patients with Crohn's disease

Reference	Year	No. of patients	Extent of disease	Method	Recurrence rate (%)	
					5 years	10 years
Higgins and Allan ¹⁵	1980	227	Distal ileum	Reoperation rate	18	36
Whelan <i>et al.</i> ¹⁶	1985	615	Mixed	Reoperation rate	—	53
Michelassi <i>et al.</i> ¹⁷	1991	1379	Mixed	Reoperation rate	20	34
Poggioli <i>et al.</i> ¹⁸	1996	233	Mixed	Reoperation rate	13	39
Post <i>et al.</i> ¹⁹	1996	689	Mixed	Reoperation rate	24	41

Except during childhood, resection rates were high. Postoperative recurrence rates were moderate and decreasing, although symptomatic rates were considered and a trend towards limited resection is obvious. Perianal disease and extensive resection of the terminal ileum are useful prognostic factors and indicate an increased risk of later disease relapse, whereas resection for perforating conditions, such as palpable masses and abscesses, is predictive of a low risk of recurrence

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Risk factors related to operative mortality and morbidity in patients undergoing emergency gastrectomy

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Background: Emergency gastric resection for complicated peptic ulcer and gastric cancer is a major challenge for general surgeons. This study aimed to evaluate the results of emergency gastrectomy and to examine the factors that predict the operative outcome.

Methods: A total of 82 consecutive patients who underwent emergency gastrectomy were studied. The following variables were assessed: pathology, mortality rate, morbidity, reasons for reoperation and factors related to the outcome.

Results: There were 64 men and 18 women with a median age of 62 (range 30–90) years. The indications were bleeding and perforated gastric or duodenal ulcers in 45 and 20 patients respectively, and bleeding and perforated gastric tumours in seven and ten patients respectively. The overall mortality rate was 17 per cent ($n = 14$). The complication rate was 63 per cent and 11 patients (13 per cent) required reoperation. By multivariate analysis, age greater than 65 years and blood haemoglobin level less than 10 g/dl on admission were predictive of complications after emergency gastrectomy. Postoperative pulmonary and cardiac complications and hypotension on admission were independent risk factors associated with operative death.

Conclusion: Age more than 65 years, haemoglobin level less than 10 g/dl and hypotension on admission were associated with a poor outcome after emergency gastrectomy. The operative result was not affected by the underlying gastric pathology.

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Introduction

The first gastric resection was performed by Theodore Billroth in 1881 for an antral carcinoma¹. In the same year, Rydiger performed a partial gastrectomy for a patient with a gastric ulcer². Since then, many different methods of gastric resection and reconstruction have been developed. Nowadays, the operative mortality rate for elective gastrectomy has decreased to less than 5 per cent^{3,4}. However, with the success of medical therapy for peptic ulcers worldwide, the number of gastric resections performed by general surgeons has also declined dramatically and surgeons in training do not get enough exposure to this procedure. On the other hand, it is also well known that the hospitalization rate for complications of peptic ulcer such as perforation and bleeding has remained fairly constant over recent decades^{3,5}. Emergency gastric resection, usually for complications of peptic ulcer or occasionally for complicated gastric cancers, is associated with a significant risk of morbidity and death. However, a large series of emergency

gastrectomies has not been reported in the literature. In this study, the results of emergency gastrectomy performed over the past 11 years were examined, and the factors that predicted the operative morbidity and mortality risk were evaluated.

Materials and methods

A case record review of all patients who underwent emergency gastrectomy from 1988 to 1998 was performed. In this study, gastrectomy was defined as any form of gastric resection with or without vagotomy. Gastric resection without vagotomy referred to the removal of two-thirds of the stomach. When vagotomy was added, the resection was usually an antrectomy or hemigastrectomy.

Data for the patients were extracted from the hospital records, operative notes and clinic charts. Emergency gastrectomy was for complications of benign gastric or duodenal ulcers or gastric tumours. These complications included acute bleeding and perforation. These two

complications posed different problems for the clinicians, haemodynamic instability and sepsis respectively. Patients who presented with these two complications were evaluated separately. Patients who presented with both complications were classified according to the indication for emergency surgery. It was the policy to perform emergency gastric resection for most complicated gastric ulcers and gastric cancers. For duodenal ulcers, gastric resection was performed only if the ulcers were too large for simple closure and provided that the patients were stable during the operation. Anastomosis was either handsewn or stapled. Reconstruction after partial gastrectomy was by Billroth II gastrojejunostomy or Billroth I gastroduodenostomy. Following total gastrectomy, an oesophagojejunostomy was constructed in a Roux-en-Y fashion, either handsewn or stapled. The method of anastomosis and reconstruction was determined by the surgeon's preference.

Statistical analysis

The χ^2 test or Fisher's exact test, where appropriate, was used for univariate comparisons. Multiple logistic regression was used to incorporate all of the potential variables in the same model. Differences were considered significant when $P < 0.05$. All deaths within 30 days of operation were included in the surgical mortality rate.

Results

A total of 82 patients underwent emergency gastrectomy during the study interval. The characteristics of the patients are shown in *Table 1*. Fifty-two patients presented with gastrointestinal bleeding; 45 patients had bleeding gastric or duodenal ulcers and seven patients had gastric carcinoma. Among 30 patients who had perforation, there were 20 perforated gastric or duodenal ulcers and ten perforated gastric tumours. Twenty-four patients who developed ulcer complications (18 patients with bleeding and six patients with perforation) were known to have a previous history of peptic ulcer. A significant proportion of patients had concomitant medical problems and risk factors for surgery which included hypotension, delay to surgery, anaemia, transfusion of more than 6 units and severe peritoneal soiling^{6,7}.

Among patients who presented with bleeding, all but three had gastroscopy before surgery. These three patients had massive upper gastrointestinal bleeding and immediate laparotomy was performed. Of the other patients who underwent emergency surgery, 29 patients had uncontrolled bleeding on endoscopy; 19 patients had rebleeding after initial endoscopic haemostasis. Four patients underwent operation because bleeding gastric tumours were seen on endoscopy. The median size of bleeding and perforated benign ulcers was 2.0 (range 1–4) and 2.0 (range 1–6.5) cm

Table 1 Characteristics of patients undergoing emergency gastrectomy

	Bleeding group (n=52)	Perforation group (n=30)	Overall (n=82)
Age (years)*	63(2)	59(3)	61(2)
Sex ratio (M:F)	41:11	23:7	64:18
Pathology			
Gastric ulcer	22	9	31
Prepyloric ulcer	11	6	17
Duodenal ulcer	11	5	16
Gastric and duodenal ulcer	1	0	1
Gastric carcinoma	7	9	16
Stomal tumour	0	1	1
Comorbid illness			
Cardiovascular	20	2	22
Pulmonary	6	3	9
Renal	11	1	12
Albumin < 3g/dl	20	5	25
Risk factors for surgery			
Hypotension	24	5	29
Delay to surgery > 24 h	21	6	27
Anaemia†	33	6	39
Massive transfusion‡	37	2	39
Severe contamination	0	20	20

*Values are mean(s.e.m.). †Haemoglobin less than 10 g/dl; ‡more than 6 units

respectively. The median size of bleeding and perforated gastric tumours was 6.0 (range 2–15) and 4.0 (range 1–5) cm respectively.

Twenty-two patients presented with bleeding gastric ulcers. Twenty patients underwent partial gastrectomy. The other two patients had total gastrectomy and proximal gastrectomy. Eleven patients had bleeding from prepyloric ulcers; nine had a partial gastrectomy and two patients underwent truncal vagotomy and antrectomy. Of the 11 patients who had bleeding duodenal ulcers, six patients had a partial gastrectomy, four patients underwent vagotomy and antrectomy, and one patient required total gastrectomy because of associated gastric erosions. Emergency gastrectomy was performed for 20 patients with perforated benign ulcers. Of the nine patients who had gastric ulcers, seven had partial gastrectomy and two patients required total gastrectomy. Six patients had prepyloric ulcers and had partial gastrectomy. Five patients presented with perforated duodenal ulcers and all underwent partial gastrectomy.

Seven patients presented with bleeding from a gastric carcinoma. Five patients underwent partial or subtotal gastrectomy and two had a total gastrectomy. Another ten patients had perforated gastric tumours; nine patients underwent subtotal gastrectomy and one had total gastrectomy.

Overall, anastomosis was performed by handsewing in 40 patients and by stapler in 42. Of patients who had a partial gastrectomy, 64 had a Billroth II reconstruction and ten a Billroth I anastomosis. The median duration of operation was 150 (range 60–310) min. There was no statistically significant correlation between operative morbidity and the type of operation and reconstruction. The pathological stage for patients with gastric adenocarcinoma was stage I in

two patients, stage II in five, stage III in four and stage IV in five patients.

The overall complication rate was 65 per cent; 69 per cent for those presented with bleeding and 53 per cent for those with perforation (*Table 2*). The morbidity rate for patients who presented with bleeding gastric, prepyloric and duodenal ulcers was 77, 73 and 45 per cent respectively. For those with perforation, the complication rate was 55, 80 and 33 per cent respectively. On the other hand, the complication rate was 50 per cent in perforated gastric tumours and 87 per cent in bleeding tumours. Eleven patients required reoperations because of rebleeding (three patients), duodenal leakage (three), subphrenic abscess (one) and secondary suture of the abdominal wound (three). One patient developed splenic necrosis after total gastrectomy and required splenectomy.

Deaths are shown in *Table 2*. Causes in those who presented with bleeding were exsanguination (three patients), duodenal leakage (two), pneumonia (three), myocardial infarction (two), cardiac failure, respiratory failure and renal failure (one patient each). In those with perforation, death was due to sepsis in one patient and iatrogenic pulmonary laceration by chest tube insertion in another. The median hospital stay was 13 (range 4–140) days. Median follow-up was 9 (range 1–70) months. Of patients with gastric tumours, three patients died in the postoperative period. One patient was lost to follow-up. Seven patients died from metastasis and six patients were still alive at the last visit. Median survival was 22 (95 per cent confidence interval (c.i.) 11–35) months.

Univariate analysis revealed that age greater than 65 years, blood haemoglobin level less than 10 g/dl, hypotension on admission, preoperative blood transfusion

Table 2 Morbidity and mortality of emergency gastrectomy

	Bleeding group (n=52)	Perforation group (n=30)	Overall (n=82)
Sepsis			
Wound	7 (13)	3 (10)	10 (12)
Abdominal	5 (10)	4 (13)	9 (11)
Duodenal leak	3 (6)	1 (3)	4 (5)
Bleeding	9 (17)	1 (3)	10 (12)
Ileus	6 (12)	3 (10)	9 (11)
Systemic complications			
Cardiac	10 (19)	1 (3)	11 (13)
Pulmonary	21 (40)	7 (23)	28 (34)
Renal	4 (8)	2 (7)	6 (7)
Other	10 (19)	4 (13)	14 (17)
Reoperation	6 (12)	5 (17)	11 (13)
Death	12 (23)	2 (6)	14 (17)

Values in parentheses are percentages. Cardiac complications included dysrhythmia, heart failure and myocardial infarction; respiratory complications included atelectasis, bronchopneumonia and aspiration pneumonia; renal complications included acute renal impairment or failure; other complications included stroke in one patient, deep vein thrombosis in four patients and splenic necrosis in one patient

requirement, and total blood transfusion with 6 units or more were significantly associated with complications (Table 3). However, sex, location of the lesion, surgical delay, the presence of co-morbidity, malignancy or whether the presentation was perforation or bleeding did not correlate with the outcome. By multiple logistic regression, age greater than 65 years (relative risk (RR) 3.2 (95 per cent c.i. 1.1–9.2); $P=0.03$) and haemoglobin level less than 10 g/dl on admission (RR 3.4 (1.2–8.6); $P=0.02$) were independent predictive factors of complications after emergency gastrectomy. On the other hand, hypotension on admission (RR 7.6 (1.6–36.5); $P=0.006$), and postoperative pulmonary (RR 6.5 (1.4–30.2); $P=0.01$) and cardiac (RR 7.0 (1.2–40.7); $P=0.03$) complications were independent factors that predicted mortality risk by multivariate analysis.

Discussion

Bleeding and perforation are two major complications of benign peptic ulcer. It is well known that despite rapid advances in medical therapy for peptic ulcer, the incidence of ulcer complications remains fairly constant⁵. Bleeding is a common presentation of peptic ulcer, and occurs in up to 20 per cent of patients with chronic duodenal ulcer⁸. Endoscopy is currently the mainstay of management for rapid diagnosis and control of bleeding^{9,10}. Some evidence suggests that early surgery is preferable, especially in the elderly population¹¹. However, in most instances, surgery is used as a salvage option when haemostasis has failed or rebleeding occurs¹². In a recent series of over 3000 patients with bleeding peptic ulcer, about 2 per cent of patients had unsuccessful endoscopic treatment and about 10 per cent of patients developed rebleeding¹³. Salvage surgery was

associated with high operative risk, as the patients were often ill. In that series, salvage surgery carried a mortality rate of 18 per cent.

In general, partial gastrectomy or antrectomy is recommended for bleeding gastric ulcer¹⁴, although in critically ill patients some surgeons advocate ulcer excision and vagotomy¹⁵. The basic surgical options for bleeding duodenal ulcer lie either in partial gastrectomy, or vagotomy with oversewing of the ulcer and pyloroplasty¹. The latter may be a simpler procedure. However, the results of a randomized study showed that the two procedures carried an equal mortality risk, as vagotomy and pyloroplasty had a higher risk of rebleeding¹⁶. Perhaps, the choice should be determined by the nature of the ulcer. If the ulcer is large and the duodenum is grossly deformed, resection and closure of the duodenum may be necessary¹⁷.

Surgery is the mainstay of treatment for perforation, although medical treatment may be effective in young patients¹⁸. Patients with perforated gastric ulcers are usually recommended to undergo emergency gastrectomy¹⁹. Simple closure alone is associated with a higher rate of non-healing, and 6–15 per cent of perforated gastric ulcers are malignant²⁰. For patients with perforated duodenal ulcers, debate continues over simple closure alone or definitive ulcer surgery, although immediate definitive surgery has been shown to be safe and effective in preventing ulcer recurrence²¹. However, with the discovery of *Helicobacter pylori* in the pathogenesis of duodenal ulcer, simple closure alone plus anti-*Helicobacter* therapy is effective for most cases of perforated duodenal ulcer²². Recently, laparoscopic patch repair of perforated ulcers has been advocated^{23,24}. Gastric resection is usually reserved for giant ulcers when it is not safe to have simple closure alone¹.

Table 3 Univariate analysis of predictors of complications

	No complications (n=29)	Complications (n=53)	P*	Relative risk
Age (years)				
>65	7	27		
<65	22	26	0.02	3.5 (1.3–9.7)
Hypotension				
Yes	6	23		
No	23	30	0.03	3.2 (1.1–9.1)
Haemoglobin (g/dl)				
<10	9	30		
≥10	20	23	0.04	2.0 (1.0–3.9)
Preoperative blood transfusion				
Mean(s.d.) units	1.6(2.3)	2.7(2.3)	0.03	
Total blood transfusion (units)				
≥6	9	30		
<6	21	22	0.01	3.6 (1.4–9.5)

Values in parentheses are 95 per cent confidence intervals. *Fisher's exact test

There have been few reports on the operative risk of emergency gastric resection for individual pathology. For bleeding peptic ulcer, recent series reported that emergency gastrectomy had a mortality risk of 12–23 per cent^{3,6,14,17}. Duodenal leakage is the most dangerous complication. In the series by Millat *et al.*¹⁶, eight of 60 patients undergoing emergency gastrectomy for bleeding ulcer developed a duodenal leak with a mortality rate of 50 per cent. In the present series, the duodenal leakage rate in this subgroup of patients was 6 per cent, and two of three patients died because of leakage. Rebleeding after operation is another major complication, which may lead to death²⁵. In this series, rebleeding occurred in 17 per cent of patients with bleeding ulcers, and the mortality risk was over 30 per cent.

The mortality rate of emergency gastric resection for perforated ulcer here was comparable to that of other series. Lanng *et al.*²⁶ reported a mortality risk of 24 per cent in 41 patients with perforated benign gastric ulcer who underwent gastrectomy. In the series by Hodnett *et al.*¹⁹ the mortality rate for gastrectomy was 12 per cent, compared with 23 per cent in patients with simple closure alone. However, the low mortality risk of gastrectomy for perforated ulcers might be the result of bias in patient selection in these procedures.

This series has identified that age over 65 years is an independent factor that predicted high mortality risk after emergency gastrectomy. This is consistent with the results of a previous study in which elderly patients had a much higher risk than young patients with perforated peptic ulcers²⁷. In a study by Hewitt *et al.*²⁰ the mortality and morbidity rates of gastric resection were also significantly increased in elderly patients with perforated gastric ulcers. In a study by Branicki *et al.*⁷ age more than 60 years, concurrent illness and blood transfusion of more than 5 units were related to poor outcome after emergency operation for bleeding peptic ulcer.

The reported incidence of perforation of gastric cancer is less than 1 per cent. Few reports describe the surgical results of perforated gastric carcinoma^{28,29}. A meta-analysis from the Japanese literature that evaluated 155 patients with perforated gastric carcinoma was published recently²⁸. Emergency gastrectomy was performed in 83 per cent of patients with an operative mortality rate of only 7 per cent. The overall 5-year survival rate was as high as 40 per cent, which was directly related to the pathological stage of the disease. In another series of 34 patients with perforated cancer by Gertsch *et al.*²⁹ the resection rate was 88 per cent with an operative mortality rate of 16 per cent. Thus resection can be a potentially curative treatment for perforated gastric cancer provided that the patient's condition is stable during surgery.

In conclusion, this study demonstrated that emergency gastrectomy for bleeding and perforated peptic ulcer or gastric cancer is a treatment option, but is not without risk. It is clear that there are attendant inaccuracies with any retrospective study, but the results are clear and show that age greater than 65 years and haemoglobin level less than 10 g/dl on admission are predictive factors for postoperative complications. Hypotension on admission and development of postoperative pulmonary and cardiac complications significantly increase the operative mortality risk. As surgery for these patients carries a high risk of death and morbidity, it may be better managed by surgeons with a special interest in this area, as surgical experience is a well known predictive factor for complications in upper gastrointestinal surgery^{30,31}.

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Day-case laparoscopic fundoplication for gastro-oesophageal reflux disease

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Background: Based on a series of successful outpatient laparoscopic cholecystectomies, day-case laparoscopic fundoplication for gastro-oesophageal reflux disease was introduced in January 1997. The initial results are reported.

Methods: Inclusion criteria were American Society of Anesthesiologists grade I–II, living within 30 min travel from the hospital, and adult company at home. Initially only selected patients were offered day-case treatment, but later it was adopted as routine. The patients underwent general intravenous anaesthesia with propofol and remifentanyl, and were given ketorolac, propacetamol, droperidol and ondansetron as prophylaxis against postoperative pain and nausea. The surgical procedure was Nissen–Rosetti fundoplication or semifundoplication depending on oesophageal manometric results.

Results: Forty-five patients were included. Four patients were admitted; 41 were discharged as planned 3–8 h after operation, and five of these patients were readmitted. One underwent reoperation for necrosis of the gastric fundus. A further five patients visited the outpatient department without need for admission. At follow-up 31 patients were satisfied with the day-case treatment, five were indifferent, and five were dissatisfied because of pain. If offered a similar operation in the future, 26 patients would have preferred and seven would have accepted day-case treatment, and eight would not.

Conclusion: Outpatient laparoscopic fundoplication is safe and well tolerated by the majority of patients.

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Introduction

Day-case treatment for surgical procedures such as inguinal hernia repair and proctological surgery is both well tolerated by the patients and cost effective, as well as useful in order to reduce the length of waiting lists^{1–4}. Refined surgical and anaesthetic techniques allow even more comprehensive procedures to be performed on an outpatient basis^{1,5,6}, for example laparoscopic cholecystectomy⁷. Routines to ensure patient safety, by recognition and adequate care of postoperative complications, have been established and proven to be effective. In January 1997 laparoscopic fundoplication for gastro-oesophageal reflux disease was introduced as a day-case procedure, the main concerns being early detection and safe management of serious postoperative complications. Patient tolerance and satisfaction, as well as patient safety, were examined in this prospective observational study.

Patients and methods

The inclusion criteria for outpatient fundoplication were American Society of Anesthesiologists (ASA) grade I–II of general health, living within 30 min by car from the hospital, and the company at home of an adult person until the next morning. In the outpatient department, when the indication for surgical treatment was discussed, patients were informed about the surgical procedure, the expected postoperative course, and possible postoperative problems and complications. At a special appointment the day before the operation, this information was repeated, and also given to the patients in written form, including relevant telephone numbers as well as the private numbers of the surgeon. On the day of the operation, patients arrived at 07.00 hours, and the operation started at 08.00 hours.

Total intravenous general anaesthesia with a special focus on postoperative pain and nausea prophylaxis was used with

ketorolac 30 mg, propacetamol 2 mg, droperidol 1.25 mg and ondansetron 4 mg given intravenously to all patients. Continuous infusion of propofol (aiming at a serum level of $5 \mu\text{g ml}^{-1}$ during induction and $3\text{--}4 \mu\text{g ml}^{-1}$ during maintenance) and remifentanyl $0.1\text{--}0.3 \mu\text{g kg}^{-1} \text{ min}^{-1}$ was used throughout the procedure. Rocuronium 0.6 mg kg^{-1} was used to facilitate endotracheal intubation and fentanyl $1 \mu\text{g kg}^{-1}$ was given when the remifentanyl infusion was stopped. Long-acting local anaesthetic (20 ml bupivacaine 2.5 mg ml^{-1}) was infiltrated into the wounds. Postoperative pain was treated with paracetamol and codeine supplemented with fentanyl when needed, and nausea with metoclopramide.

The laparoscopic procedure was performed according to the principles of Nissen–Rossetti^{8,9} or as a semifundoplication (Toupet)⁸, both including posterior closure of the diaphragmatic crura. Diathermy was used for haemostasis and division of the short gastric vessels. All procedures were performed by a senior surgeon, or by a resident supervised by a senior surgeon. After operation the patients were scheduled to leave before 18.00 hours. Before departure, they had been fully mobilized and had enjoyed an ordinary sandwich meal without any dietary restrictions. They were examined by the surgeon in charge of the operation. They were given a prescription for paracetamol and codeine (20 tablets) and metoclopramide (ten suppositories). Patients were routinely contacted by telephone by the surgeon on the same evening, by both the surgeon and the anaesthetist the next day, and by the surgeon on subsequent days, if necessary.

Patient tolerance for day-case treatment was recorded by the anaesthetists and surgeons responsible for the treatment. A telephone call 1 week or more after the operation, together with clinical follow-up at a median of 4 weeks after surgery, were the basis for outcome assessment. Alternative answers for patient satisfaction were: excellent, good, fair and poor. Patients were also asked for a preference if they were to have a similar procedure in the future.

Results

During the first year only five of 12 eligible patients were offered day-case treatment. In March 1998 it was introduced as routine for patients fulfilling the inclusion criteria, and to June 1999 a further 40 patients were included, 21 women and 24 men (median age 42 (range 23–69) years). Forty-two patients underwent a Nissen–Rossetti procedure and three a semifundoplication. No additional procedures such as cholecystectomy or adhesiolysis were performed. There were no conversions to an open operation.

Forty-one patients were discharged as planned 3–8 (mean(s.d.) 6.6(0.9)) h after the operation. Thirty-five

patients were escorted by a relative; six went home by taxi. Twelve patients described the transport home as arduous, although acceptable, because of pain ($n=5$), fatigue ($n=4$) or nausea ($n=3$). Four patients were admitted directly from the outpatient department, two for pain and fatigue, one because of nausea, and another developed a small pneumothorax. A total of six patients (15 per cent) experienced significant nausea and vomiting.

Of the discharged patients, 21 had an uneventful postoperative course with only minor postoperative problems, which were no more than they had expected according to the preoperative information. Twenty patients experienced various degrees of nausea, pain, dysphagia and fatigue. Five patients were readmitted. One of them experienced increasing abdominal pain during the first night and was readmitted early the next morning. She underwent reoperation after 2 days and had a necrotic gastric fundus, which was resected. In two other patients, readmitted on days 1 and 2 because of pain, no specific pathology was recognized. One patient had severe retching the first day and stayed for one night, and another patient was readmitted on day 5 because of dysphagia and inadequate oral nutrition. Five other patients visited the hospital during the first days after the operation without the need for readmission: one patient the same evening because of urinary retention, three because of pain and dysphagia, and one because of a subcutaneous port-site haematoma. In the patients with pain and nausea who were not readmitted, the symptoms were moderate or mild; they were treated successfully with analgesics or antiemetics as prescribed, without any need for special medical consultation. The symptoms subsided within 1–4 days in most of these patients, but two had some pain for 2 and 4 weeks.

At follow-up 36 patients were satisfied with the day-case treatment, although five of them would have preferred to stay the first night in hospital, as they might have felt safer that way. Five patients would have preferred an inpatient procedure because of pain, but one of these refused admission despite several offers during the telephone contacts.

Thirty-eight of the discharged patients were satisfied with the preoperative information and felt well prepared for the postoperative period. Only two of the patients did not feel comfortable about the routines for contact back to the hospital, and they were also dissatisfied with the follow-up by the hospital during the early postoperative course.

When asked for preference if they were to have a similar surgical procedure in the future, 26 of the discharged patients would have preferred and seven would have accepted a day-case operation. Eight patients would have preferred an inpatient procedure.

Discussion

Outpatient surgery has been performed since the beginning of this century both for the benefit of patients and for economical reasons¹. Ambulatory surgery accounts for about 24 per cent of elective surgical procedures in Norway (1996)³, and for 30 per cent in UK (1995)¹. This rate is expected to increase, especially for gastroenterological conditions¹, and is motivated by improved surgical and anaesthetic techniques as well as cost-efficiency considerations^{6,10}.

Between 1994 and 1997, 500 outpatient laparoscopic cholecystectomies were performed in this hospital, amounting 90 per cent of elective cholecystectomies, with an admission rate of 6 per cent and a readmission rate of less than 5 per cent⁷. Only 1 per cent of these patients were dissatisfied with the day-case treatment. In addition to the minimally invasive surgical technique, the main reason for this success was probably a refined anaesthetic technique with propofol, short-acting opioids and non-steroidal anti-inflammatory drugs⁶. Based on this experience, laparoscopic fundoplication for gastro-oesophageal reflux disease was introduced as a day-case procedure, initially in highly selected patients, and later adopted as routine for eligible patients.

Preoperative information and close follow-up are the cornerstones of the outpatient fundoplication concept, as for other outpatient surgical treatment settings^{4,10,11}. The information should be comprehensive and also provided in a written form to ensure that patients are aware of the various postoperative problems and will be able to recognize unexpected symptoms of possible complications. Before departure from the outpatient department the patients are examined by the surgeon responsible for the operation. The follow-up by telephone by the surgeon, both routinely and by supplementary calls if needed, is much appreciated by the patients.

There was one serious complication: a necrosis of the part of the gastric fundus included in the fundoplicate. The patient experienced severe pain, and she contacted the clinic the next morning, according to routines. Thus, even in an outpatient treatment setting, with thorough preoperative information and safe and easy routines for contact back to the hospital and readmission, a complication like this did not preclude the continuation of this day-case surgery programme for laparoscopic fundoplication. Generally, the frequency of serious postoperative complications after laparoscopic fundoplication seems low. Grade 2 complications according to the Toronto classification of complications¹² (potentially life threatening, resulting in twice the median stay for the uncomplicated procedure, but not resulting in residual disability) occurred in 1–5 per cent of patients in ten series of laparoscopic fundoplication

comprising a total of 1216 patients^{13–22}. The most feared complication in an ambulatory setting is acute postoperative haemorrhage. In the literature^{13–22}, however, there is only one reported case of postoperative bleeding²². Even the slightest clinical suspicion of bleeding should preclude discharge.

In 1997 Shauer *et al.*²³ reported a consecutive series of nine patients treated with outpatient laparoscopic fundoplication without readmission, and Milford and Paluch⁵, also in 1997, reported no readmission and no patients expressing dissatisfaction in a consecutive series of 61 patients. Five of the present series of patients were dissatisfied because of excessive pain. No irregularity, either in the anaesthetic or the surgical procedure, could explain this. In two of these patients who were readmitted there were no signs of intra-abdominal pathology, and the pain resolved without specific medical intervention.

Six (15 per cent) of the 41 patients had postoperative nausea or vomiting, compared with the usual frequency of 40–60 per cent²⁴. No patient had a nasogastric tube, and all enjoyed a meal of solid food before discharge. The main reasons for the low frequency of postoperative nausea are probably use of non-opioid pain prophylaxis with propacetamol, ketorolac and local anaesthesia as well as the prophylactic use of antiemetics⁶.

It is a matter of concern that some of the patients felt unsafe at home. This fact may be a consequence of the policy of detailed preoperative information about complications which was regarded as necessary in order to ensure early readmission in case of serious complications such as haemorrhage. The patient information may be influenced by the good result in this initial series.

In this setting, day-case laparoscopic fundoplication seems to have been both safe and well tolerated by the majority of patients, and it is projected that more than 95 per cent of laparoscopic fundoplications may be scheduled as same-day surgery.

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Clinicopathological study of multiple superficial oesophageal carcinoma

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Background: Recently, the diagnosis of superficial oesophageal carcinoma has increased markedly in Japan as a result of advances in endoscopy. A number of these carcinomas have proved to be multiple.

Methods: Some 359 patients with superficial squamous cell carcinoma of the oesophagus who underwent oesophagectomy ($n=276$) or endoscopic mucosal resection (EMR) ($n=83$) were reviewed retrospectively. The clinicopathological features of patients with multiple superficial oesophageal carcinoma were compared with those of patients with a single superficial oesophageal carcinoma.

Results: Of the 359 patients, 99 (28 per cent) had multiple superficial oesophageal carcinoma. The male:female ratio in patients with multiple carcinoma was 98:1, compared with 5.3:1 for those with a single carcinoma ($n=260$) ($P=0.0001$). The incidence of tobacco and alcohol use was significantly higher in the patients with multiple carcinoma than in those with a single carcinoma ($P=0.04$ and $P=0.03$ respectively). The incidence of pharyngeal malignancy was also significantly higher in patients with multiple carcinoma ($P=0.02$).

Conclusion: The high incidence of multiple superficial oesophageal carcinoma indicates a need for careful evaluation of the oesophagus at the time of initial diagnosis, treatment and follow-up for superficial oesophageal carcinoma. Male sex, smoking, alcohol use and the presence of pharyngeal malignancy are high-risk factors for multiple superficial oesophageal carcinoma.

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Introduction

In recent years, as a result of technical advances in diagnostic procedures such as the Lugol solution staining technique^{1,2} at oesophagoscopy, the frequency of diagnosis of superficial oesophageal carcinoma, defined as carcinoma with invasion limited to the submucosa, has increased markedly in Japan, and many of these have been found to be multiple. Recent advances in surgical treatment³ have increased the long-term survival rate of patients with superficial oesophageal carcinoma, and endoscopic mucosal resection (EMR) for cancer limited to the lamina propria mucosae has yielded a better quality of life after treatment^{4–6}. Accordingly, residual secondary lesions have become a clinical problem.

This study investigated the clinicopathological features of multiple superficial oesophageal carcinoma in comparison with single superficial oesophageal carcinoma, and identified the characteristics of secondary lesions in patients with multiple carcinoma.

Patients and methods

Between 1962 and 1997, surgical resection or EMR was performed in 386 patients with superficial oesophageal carcinoma (359 squamous cell carcinomas, seven adenosquamous carcinomas, seven carcinosarcomas, four undifferentiated carcinomas, four adenocarcinomas, three malignant melanomas, one basaloid carcinoma, one adenoid cystic carcinoma). In this study, a total of 359 patients with superficial squamous cell carcinoma of the oesophagus who underwent oesophagectomy (276 patients) or EMR (83) without preoperative treatment was evaluated retrospectively.

Superficial oesophageal carcinoma was defined as a lesion confined to the mucosa or submucosa (Union Internationale Contra la Cancrum pathological tumour node metastasis (pTNM) classification⁷: pT_{is} or pT₁). Multiple superficial oesophageal carcinoma was defined histologically as follows: (1) each cancerous lesion was located individually; (2) the distance between each lesion was greater than 1 cm;

(3) each lesion was fully exposed to the oesophageal lumen; (4) the main lesion was defined as the most advanced, in terms of the depth of invasion and size, and any other lesions were designated as secondary; (5) lesions appearing more than 1 year after initial treatment of the primary lesion were categorized as metachronous multiple superficial oesophageal carcinoma. The clinicopathological features of patients with multiple superficial oesophageal carcinoma were compared with those of patients with a single superficial oesophageal carcinoma. The depth of tumour invasion was determined according to the diagnostic criteria set by the Japanese Society for Esophageal Disease⁸: invasion limited to the epithelium (ep), invasion confined to the lamina muscularis mucosae (mm), or invasion confined to the submucosa (sm). For histological examination, 2-mm sections were used for tissue specimens obtained at EMR, and 1-cm sections for surgical resection specimens.

To elucidate positive risk factors for multiple superficial oesophageal carcinoma, the incidence of multiorgan tumours, family history of cancer, and tobacco and alcohol use were subjected to a retrospective statistical analysis. Information on aetiological factors was obtained from the hospital notes of each patient.

Differences between patients with multiple superficial oesophageal carcinoma and those with a single superficial oesophageal carcinoma were analysed with the χ^2 test, Fisher's exact probability test and Student's *t* test. Survival rates were calculated according to the life-table method. Survival curves were computed by means of the Kaplan-Meier method⁹. The difference between the two survival curves was analysed with the log rank test¹⁰ and the Cox-Mantel test¹¹.

Results

Of 359 patients with superficial squamous cell carcinoma of the oesophagus, 99 (28 per cent) had multiple superficial oesophageal carcinoma; 83 (84 per cent) of the 99 patients underwent surgical resection and 16 (16 per cent) had EMR. Metachronous multiple superficial oesophageal carcinoma was later discovered in three patients (1 per cent) who underwent oesophagectomy, and in four (5 per cent) who had EMR.

The male:female ratio of patients with multiple carcinoma (98:1) was significantly higher than that of the 260 patients with a single carcinoma (5.3:1) ($P=0.0001$). The incidence of tobacco use among patients with multiple carcinoma was significantly higher than in patients with a single carcinoma ($P=0.04$). The incidence of alcohol use was also significantly higher in patients with multiple carcinoma ($P=0.03$). The difference in average age between the two groups was not significant. Twenty-eight (28 per

cent) of the patients with multiple carcinoma and 68 (26 per cent) of those with a single carcinoma had third-degree or closer blood relatives with cancer. The incidence of a positive family history was not significantly different between the two groups (Table 1).

Of the 99 patients with multiple carcinoma, 52 (53 per cent) had primary malignancies in other organs, and eight of them had triple cancers in three separate organs. Of the 260 patients with a single carcinoma, 90 (35 per cent) had primary malignancies in other organs. Fourteen had triple cancers in three separate organs and one had quadruple cancers in four separate organs. The incidence of multifocal tumours was significantly higher in patients with multiple carcinoma than in those with a single carcinoma ($P=0.002$) (Table 1). Table 2 compares the presence of synchronous or metachronous multiple organ tumours in the multiple and single groups. The incidence of associated pharyngeal cancer in patients with multiple carcinoma was significantly higher than that in patients with a single carcinoma ($P=0.02$).

Table 1 Characteristics of patients with multiple or single superficial carcinoma of the oesophagus

	Multiple (n=99)	Single (n=260)	P
Age (years)*	60.6(8.4)	62.3(9.1)	0.101
Sex ratio (M:F)	98:1	219:41	0.0001§
Tobacco use (%)	84	74	0.04§
Smoking habit*†	902.7(706.8)	711.2(597.1)	0.01‡
Alcohol use (%)	85.8	75.3	0.03§
Drinking habit of more than 5 days per week (%)	84.8	65.0	0.01§
Family history of cancer (%)	28.2	26.1	0.68§
Multiple primary cancers (%)	53	35	0.002§

*Values are mean(s.d.); †Number of cigarettes smoked per day $\times$ number of years of smoking; ‡*t* test; § χ^2 test

Table 2 Occurrence of synchronous or metachronous multiple organ tumours in patients with multiple and single superficial oesophageal carcinoma

Site of multifocal lesions	Multiple (n=99)	Single (n=260)	P*
Head and neck	34 (34)	42 (16)	0.02
Pharynx	25 (25)	20 (8)	0.02
Tongue	4 (4)	6 (2)	0.37
Oral cavity	2 (2)	6 (2)	0.86
Larynx	1 (1)	6 (2)	0.42
Thyroid	2 (2)	4 (2)	0.36
Stomach	15 (15)	37 (14)	0.44
Lung	2 (2)	4 (2)	0.10
Colorectum	4 (4)	10 (4)	0.93
Other	5 (5)	10 (4)	0.61

Values in parentheses are percentages. *Fisher's exact probability test

Differences in pathological features (size, location, depth of invasion, histological grading, vascular invasion and lymph node metastasis) between the groups were not significant. A comparison of lymph node metastasis was made from surgically resected patients. The cumulative 5-year survival rates were 72 and 73 per cent for patients with multiple and single carcinoma respectively. The difference between the survival curves was not significant.

Seventy-four patients (75 per cent) with multiple superficial oesophageal carcinoma had two lesions in the

Table 3 Number of lesions of multiple superficial oesophageal carcinoma

No. of lesions	No. of patients
2	74
3	16
4	3
5	2
6	2
7	1
8	1
Total	99

Table 4 Maximum diameter of 146 secondary lesions

Maximum diameter of lesion (mm)	No. of lesions
5.0 or less	49 (34)
5.1–10.0	46 (32)
10.1–20.0	27 (18)
20.1–30.0	14 (10)
30.1–40.0	5 (3)
40.1–50.0	5 (3)

Values in parentheses are percentages

oesophagus, 16 (16 per cent) had three, and nine (9 per cent) had four or more. A total of 146 secondary lesions was evident in the 99 patients with multiple superficial oesophageal carcinoma (Table 3). Ninety-four (64 per cent) of the secondary tumours were intraepithelial (ep), 38 (27 per cent) showed invasion into the mucosal layer (mm) and 14 (10 per cent) had reached the submucosal layer (sm). The maximum diameter of a lesion was less than 1 cm in 95 (66 per cent) of the 146 lesions (Table 4).

The secondary lesions were located proximal to the main lesion in 59 per cent of cases. The mean(s.d.) distance between the main tumour and the secondary lesion was 3.0(2.1) cm, and the distance between the main tumour and the secondary lesion was less than 3.0 cm in 66 per cent of the 146 lesions (Fig. 1).

Discussion

In the past, when oesophageal carcinomas were discovered, 90 per cent were advanced carcinomas associated with a predictably poor prognosis¹². However, as a result of the increased number of instances of early detection occurring due to advanced diagnostic techniques^{1,2}, a minimally invasive procedure (EMR) became available for the treatment of cancer limited to the lamina propria mucosae^{4–6}. However, such a procedure poses a more serious problem than surgical resection in the simultaneous and metachronous treatment of multiple carcinomas.

The incidence of multiple oesophageal carcinoma was reported as 18.8 per cent by Mizobuchi *et al.*¹³ and as 16.7 per cent by Sato *et al.*¹⁴ in patients without preoperative treatment. This is lower than the 28 per cent incidence of superficial oesophageal carcinoma in the present study. However, if it is assumed that multiple superficial oeso-

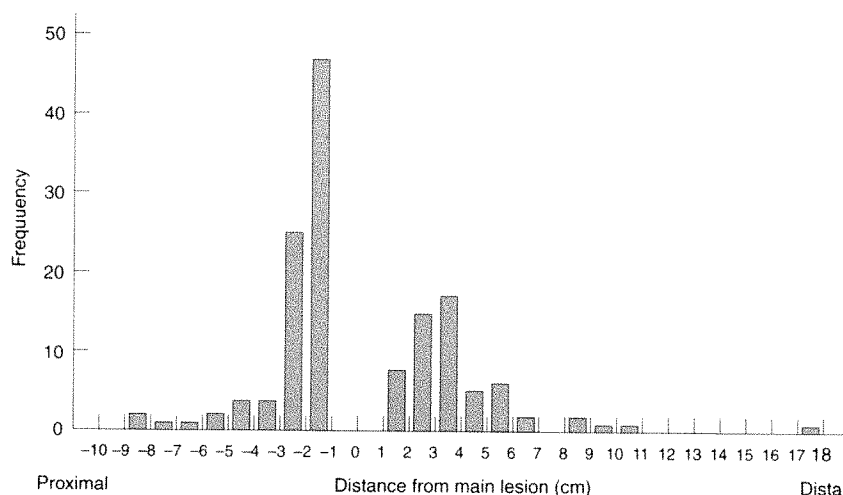


Fig. 1 Distance between the main lesion and the secondary lesion ($n = 146$). Mean(s.d.) distance 3.0(2.1) cm

phageal carcinoma lesions fuse into a single lesion as they progress, it follows that fewer multiple advanced cancers are discovered. The present finding that the secondary lesions existed within 3 cm of the main lesion in more than half of the patients supports this theory.

The high incidence of multicentricity and the relatively wide distribution of small secondary lesions in patients with superficial oesophageal carcinoma necessitates careful preoperative investigation. To this end, Lugol iodine staining should be included in the preoperative endoscopic examination, and areas that do not stain with Lugol solution must be subjected to biopsy. In patients who undergo surgical resection it is advisable to confirm negative surgical margins immediately by undertaking Lugol staining in surgical specimens¹⁵.

The high frequency of metachronous multiple superficial oesophageal carcinoma discovered by EMR suggests the probable existence of occult cancerous lesions that are not identified as the unstained area with Lugol solution on preoperative endoscopy. Careful follow-up is required to avoid missing metachronous multiple carcinoma in patients treated by EMR.

It is generally believed that cigarette smoking and alcohol are positively associated with cancers of the upper digestive tract¹⁶⁻¹⁸. In the present series the incidence of smoking and drinking was significantly higher among patients with multiple superficial oesophageal carcinoma than in those with a single superficial lesion. In addition, the incidence of pharyngeal malignancy was higher in patients with multiple superficial oesophageal carcinoma. A possible explanation is that the pharynx is easily exposed to external irritation. In addition, there is strong and consistent evidence of a positive association between tobacco and alcohol use and cancer of the pharynx^{19,20}. These results indicate that both alcohol use and cigarette smoking may act as initiators in the genesis of multiple superficial oesophageal carcinoma.

In conclusion, the high incidence of multiple superficial oesophageal carcinoma points to a need for careful evaluation of the oesophagus at the time of initial diagnosis, treatment and follow-up for superficial oesophageal carcinoma. Male sex, smoking, alcohol use and the presence of pharyngeal malignancy are considered to be high-risk factors for multiple superficial oesophageal carcinoma.

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Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma

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Background: Transhiatal resection for oesophageal cancer is a major operation with potentially severe physical, emotional and social consequences. The aim of this study was to assess various aspects of quality of life in long-term survivors following oesophageal resection for cancer.

Methods: Between January 1993 and May 1996, 100 consecutive patients with cancer of the oesophagus or oesophagogastric junction underwent a potentially curative transhiatal oesophagectomy. Patients with a minimum follow-up of 2 years and with no tumour recurrence ($n=35$) were mailed questionnaires which consisted of: (a) the Short Form-36 Health Survey to assess general quality of life, (b) an adapted Rotterdam Symptom Checklist to assess disease-specific quality of life, and (c) additional questions about other effects of the operation.

Results: All patients returned the questionnaire. General quality of life was comparable with reference values for the same age group. However, more than half of the patients still experienced at least some early satiety, fatigue, dysphagia, heartburn and/or psychological irritability. Nine of 13 patients who worked in paid employment before operation continued to do so.

Conclusion: Patients who survive 2 years or more after transhiatal oesophageal resection for cancer can lead satisfactory lives. Although some residual symptoms may persist, their general quality of life is similar to that of healthy individuals of the same age.

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Introduction

In Western countries, the incidence of adenocarcinoma of the oesophagus and of the oesophagogastric junction has risen dramatically over the past two decades^{1–3}. On average, 2- and 5-year survival rates after oesophagectomy for carcinoma of the oesophagus or oesophagogastric junction are 21 and 18 per cent respectively⁴. Earlier detection of carcinoma, improved operation techniques and advanced postoperative care have improved the 5-year survival rate, thereby increasing the number of long-term survivors⁵.

Long-term survival rates for cancer surgery should be interpreted together with postoperative results of quality of life (QoL). Most tumour recurrences after oesophagectomy occur in the first 2 years after operation. Thereafter, patients have a relatively good life expectancy.

Transhiatal oesophageal resection with gastric tube reconstruction is a major operation with potentially severe physical and emotional effects, and serious consequences

for QoL. Knowledge about the impact of the operation on QoL could help physicians inform patients more accurately about what to expect in the future. Only a few studies have evaluated QoL in long-term survivors of oesophageal resection for cancer^{6–8}. They have focused predominantly on symptoms such as gastro-oesophageal reflux, gastric emptying, alimentary discomfort and dysphagia^{6–8} or on daily activities^{6,7}. However, these studies did not take other important factors such as emotional health or employment into account. Also, little is known about which physical and emotional symptoms are the best predictors of overall QoL in patients with cancer. Furthermore, earlier research showed only weak relationships between dysphagia^{9,10} or swallowing problems¹¹ and overall QoL. Studies into relationships between other disease- or operation-related factors and QoL have rarely been performed.

The aims of the study were to assess QoL in patients who underwent transhiatal oesophageal resection and gastric tube reconstruction with a minimum follow-up of 2 years

and to investigate relationships between QoL, physical and emotional symptoms, and disease- and operation-related factors.

Patients and methods

Patients

To eliminate the effects of different operative techniques or additional treatments, a relatively homogeneous patient sample was identified. Patients who underwent a potentially curative transhiatal resection with gastric tube reconstruction were included. Patients who had received (neo)adjuvant therapy were excluded. Between January 1993 and May 1996, 100 consecutive patients fulfilled these inclusion criteria. In May 1998, 43 of these patients were alive and had a minimum follow-up of 2 years, 55 had died and two were lost to follow-up. Of the 43 surviving patients, seven had locoregional tumour recurrence or distant metastases and one had a second primary tumour of the ileum. These patients were excluded from the study. The remaining 35 patients were asked by their surgeon for written informed consent. All 35 patients agreed to participate in the survey. The study was authorized by the Medical Ethics Board of the Academic Medical Centre in Amsterdam.

Patients' records were analysed for age at time of survey, length of postoperative survival, sex, preoperative dysphagia, tumour location, pathology, and duration of postoperative intensive care and hospital stay. Details of the study population and clinical data are summarized in *Table 1*.

Quality of life

QoL was assessed by mailed self-report questionnaires. General QoL was assessed by the Medical Outcomes Study 36-item Short Form Health Survey (SF-36)¹². The SF-36 is a well validated, internationally used instrument. It is divided into eight subscales: general health, physical functioning, role limitations due to physical health problems, bodily pain, vitality, social functioning, role limitations due to emotional problems, and general mental health. All raw scales are linearly converted to a scale of 0–100, with higher scores indicating higher levels of QoL. From the eight SF-36 subscales a physical component score and a mental component score were constructed. The component scores have a mean of 50 and a standard deviation of 10 in the general US population¹³. Disease-specific QoL was measured with the Rotterdam Symptom Checklist, a self-report questionnaire designed for use in patients with cancer¹⁴. The original Rotterdam Symptom Checklist was adapted by adding nine physical symptoms specific to

Table 1 Demographic and clinical data

	No. of patients (n=35)
Age at time of survey (years)*	66.4 (42–87)
Postoperative survival (years)*	3.5 (2.1–5.4)
Sex	
Male	28
Female	7
Dysphagia to solid food before operation	22
Tumour location	
Mid-oesophagus	3
Distal oesophagus	20
Oesophagogastric junction	12
Pathology	
Histology	
HGD in Barrett's oesophagus	2
Adenocarcinoma	27
Squamous cell carcinoma	6
pTNM classification	
pT _{1a} N ₀ M ₀	2
pT _{1b} N ₀ M ₀	9
pT ₂ N ₀ M ₀	5
pT ₂ N ₁ M ₀	1
pT ₃ N ₀ M ₀	8
pT ₃ N ₁ M ₀	10

*Values are mean (range). HGD, high-grade dysplasia; pTNM, patho-

oesophageal carcinoma (e.g. dysphagia) and omitting seven less relevant physical items (e.g. lower back pain). The adapted Rotterdam Symptom Checklist contained 40 items, covering 25 physical items, seven psychological items and eight activities of daily living. Answers were rated on a four-point response scale. Higher scores indicated more complaints and poorer QoL. Patients were asked to rate their current overall QoL on a visual analogue scale: a horizontal line ranging from 0 (worst QoL) to 100 (best QoL). Additional questions were asked to assess body-weight, dysphagia, location of dysphagia and food intake (seven items), body image (four items), employment status and finances (five items), and fear of recurrent disease and future plans (eight items).

Statistical analysis

All data were checked for normal distribution as judged by graphical assessment and the Kolmogorov–Smirnov test for normality. Results indicated that the individual items of the Rotterdam Symptom Checklist were skewed, but that the subscales of the SF-36 and the Rotterdam Symptom Checklist showed normal distribution. Therefore, parametric tests were performed, except for individual items.

SF-36 subscale scores were compared with reference values reported by Aaronson *et al.*¹⁵ for a national popula-

tion in the same average age group as the study sample (61–70 years). The physical and mental component scores were compared with reference values reported by Ware *et al.*¹³ for a Dutch national sample between 18 and 74 years of age, because no data were available on the physical and mental component scores by age group. To test for differences between patient and population reference scores, *t* tests were performed. Because of multiple testing, $P \leq 0.01$ was considered statistically significant.

To investigate relationships between physical and emotional symptoms and overall QoL, stepwise multiple regression with backwards elimination was performed to determine which Rotterdam Symptom Checklist symptoms were most associated with current overall QoL as measured by visual analogue scale scores. To examine relations between QoL and disease- or operation-related factors, Pearson product moment correlations were calculated between SF-36 component scores and visual analogue scale scores on the one hand and length of survival, pathology, duration of hospital stay and duration of intensive care stay on the other. Relations between individual items of the Rotterdam Symptom Checklist and disease- and operation-related factors were also examined, calculating Spearman rank correlations. Following the recommendations of Cohen¹⁶, only moderate to high correlations ($r > 0.40$) are reported.

All analyses were conducted using SPSS version 8.0 (SPSS, Chicago, Illinois, USA).

Results

Quality of life

SF-36 subscale and summary scores are presented in Table 2. Patients' SF-36 subscale scores were comparable with or better than the reference values for the same age group¹⁵. The summary physical component score was lower than the reference value, whereas the summary mental component score was higher than that for the national sample of adults aged 18–74 years¹³. Results from the Rotterdam Symptom Checklist in Table 3 show that the most frequently reported complaint was a sensation of early satiety during a meal, mentioned by 27 patients. Additionally, more than half of the patients experienced fatigue, dysphagia, psychological irritability and/or heartburn. Problems with activities of daily living such as walking, self-care and light household chores were infrequent (one patient; data not shown). When asked to rate their current overall QoL on a visual analogue scale, patients scored a mean of 73 (range 20–100), with 29 patients rating 60 or higher.

Table 2 SF-36 subscale and summary scores

Category	Patient population	Reference values	<i>P</i> ‡
General health	68.6(24)	61.7(20)*	0.02
Physical functioning	81.8(20)	71.7(26)*	0.01
Role (physical)	76.6(34)	67.3(41)*	0.10
Bodily pain	69.8(31)	70.5(25)*	0.44
Vitality	72.1(26)	67.7(20)*	0.11
Social functioning	83.6(22)	82.0(25)*	0.36
Role (emotional)	92.9(16)	81.1(35)*	0.01
Mental health	81.3(21)	76.9(18)*	0.06
Physical component score	44.2(7.8)	49.7(9.3)†	<0.001
Mental component score	56.9(6.6)	52.1(9.6)†	<0.001

Values are mean(s.d.). *Data reported for the age group 61–70 years by Aaronson *et al.*¹⁵; †data reported for a national sample of adults aged 18–74 years by Ware *et al.*¹³. ‡*t* test

Table 3 Adapted Rotterdam Symptom Checklist quality of life scores for the ten most prevalent complaints

Symptom	1 Not at all	2 A bit	3 Somewhat	4 Very much
Early satiety after meal*	7	11	13	3
Fatigue	12	14	6	3
Dysphagia*	14	9	9	2
Irritability	14	17	2	2
Heartburn*	17	9	6	2
Loss of energy	19	11	4	1
Diarrhoea	20	8	3	4
Breathlessness	20	9	4	2
Bloated feeling	20	11	3	1
Worry	22	9	1	3

*Data missing for one patient

Body-weight, dysphagia and body image

Compared with their body-weight 1 year before operation, patients reported having lost a mean(s.d.) of 8.5(9.1) (range –24 to 15) kg but, compared with their weight at discharge, patients indicated a mean(s.d.) weight gain of 3.3(7.3) (range –18 to 15) kg. Two or more years after operation, 21 patients reported dysphagia (compared with 22 patients before operation). The majority of these patients (13) had dysphagia for solid food high in the throat at the site of the anastomosis. Food intake ranged from 2 to 6 (mean 3.3) meals a day.

Body image was not seriously affected by the operation. A majority of 30 patients did not feel unattractive, although 11 patients considered their appearance was affected adversely by the operation. None of the patients avoided people because of the scars.

Work, finance, fear of recurrent disease and future plans

Before the operation, 22 patients were retired and 13 were in paid employment. At the time of the survey, two patients had been unable to continue working and two had retired. The other nine patients continued working, albeit sometimes with fewer hours ($n=3$) or in an adjusted situation ($n=3$). Ten patients still had additional expenses related to the disease and its treatment. Costs included expenses for new clothes, adjusted beds, special food, complementary therapy and home care. One patient had had trouble obtaining funeral insurance.

Most patients (33) were convinced that they had been cured and 30 patients believed they had a normal life expectancy. However, 14 patients worried that the disease might recur.

Patients with high-grade dysplasia

The study included two patients who underwent oesophageal resection for high-grade dysplasia in Barrett's oesophagus. The results of these two patients with respect to the SF-36 summary physical and mental component scores were similar to those of patients who have undergone operation for invasive cancer. In concordance with the majority of the other patients, both patients with high-grade dysplasia were convinced that they had been cured, believed they had a normal life expectancy and did not worry that the disease might return.

Relationships between quality of life and other factors

Results of the regression analysis showed that physical and emotional symptoms on Rotterdam Symptom Checklist explain 59 per cent of the variance of overall QoL measured by the visual analogue scale. Significant associations were found for fatigue, worry and psychological irritability.

Prolonged hospital stay after the operation was correlated with lower overall QoL scores on the visual analogue scale ($r=0.46$, $P=0.01$), whereas length of survival was negatively correlated with the SF-36 summary physical component score ($r=-0.46$, $P=0.01$). No other significant correlations between disease- or surgery-related factors and QoL were found.

Discussion

In this study the QoL in long-term survivors after oesophagectomy for cancer was evaluated by mailing a questionnaire to patients with a minimum follow-up of

2 years and no evidence of recurrent disease at the last evaluation. The most striking finding was that these patients reported a similar or even better QoL than a reference group of the same age. In particular, emotional well-being was better than in the reference group. This relatively high QoL is somewhat surprising because more than half of the patients still experienced a number of symptoms, including early satiety, fatigue, dysphagia, heartburn and/or irritability. A possible explanation for the relatively high QoL despite persisting symptoms could be that patients confronted with a life-threatening or chronic illness are faced with the necessity to accommodate to the disease. It has been suggested that this process may lower internal standards (so-called 'response shift')¹⁷. As a result, patients might rate the same condition better than they would have if they had not experienced a serious illness. The patients in the present study have recovered from a major operation and have battled with cancer. Furthermore, they were most probably well informed and knew the odds of surviving oesophageal cancer, but are now long-term survivors. Consequently, they may report better QoL, and especially better emotional well-being, than the healthy population. Another possible explanation relates to sex differences in QoL measurement. The present sample consisted predominantly of men, whereas the SF-36 reference values are based on a mixed sample of men and women. Women generally report lower QoL than men¹⁵. Thus, the higher rating of QoL in the present study may be due partially to the predominance of men in the sample. Finally, it is possible that the QoL data are biased because of the applied selection procedure: patients might have reported more positive QoL because they were asked to participate by their surgeon. Additionally, it was found that the summary physical component score was lower than that of the reference group of adults aged 18–74 years. This difference is probably caused by the fact that the mean age of the study group was 66 years.

The SF-36 mental health, general health and role functioning scores were similar to those found by McLarty *et al.*⁶. However, the vitality, physical functioning and pain scores were much better than those found by McLarty *et al.* These differences may be a result of the different operative techniques used in the latter study: mainly Ivor Lewis resection (72 per cent), but also transhiatal (13 per cent), extended (4 per cent), thoracoabdominal (4 per cent) and others (8 per cent). Some of the differences could also be explained by the fact that the reference value for vitality is higher in the Netherlands than in the USA¹³.

Early satiety during a meal was the prevailing symptom among the present patients. This finding is in line with a previous study by Collard *et al.*⁸, who reported alimentary

discomfort in 11 of 17 patients who were disease free after oesophageal resection. Such discomfort is probably related to the small capacity of the oesophageal substitute and the increase in intragastric pressure in response to distension as a result of gastric tube reconstruction. Furthermore, a disrupted humoral enterogastric inhibitory reflex after oesophageal resection may contribute to disturbed gastric emptying and dumping-like symptoms¹⁸.

If patients were employed before the operation, the majority of cancer-free patients resumed occupational activity, which also confirms previous data¹².

Patients' views on cure and life expectancy seem to be somewhat contradictory: on the one hand, the vast majority of patients are convinced of being cured; on the other hand, more than one-third of patients worried that the disease might return. A possible explanation is that patients believe that they are cured as long as the disease has not recurred. It could be possible that the phrasing of the questions was not sufficiently clear to make this distinction.

The results of the regression analysis revealed interesting information, although it is acknowledged that the sample size was small and the result needs to be validated in a larger study group. The finding that the most prevalent disease-specific symptoms, as measured by the Rotterdam Symptom Checklist, were a poor predictor of overall QoL is in line with previous publications on the subject. Similarly, Blazeby *et al.*⁹, Barr and Krasner¹⁰ and van Knippenberg *et al.*¹¹ reported weak correlations between swallowing problems and QoL in patients with oesophageal cancer. It is possible that patients have adapted to the dysphagia and early satiety after a meal, so that these symptoms have less impact on their current QoL. The findings that fatigue and emotional aspects such as worry and psychological irritability have a high correlation with overall QoL is a new finding in this area of research. Surgeons should therefore inform patients about the emotional postoperative aspects of the operation as well as the physical effects. The finding that length of survival was inversely correlated with the physical component score might be related to the age of the patients. It is well known that older people tend to have lower QoL than younger people. Because patients with longer survival are more likely to be older than those with shorter survival, it is not surprising that length of survival is inversely correlated to QoL.

In conclusion, patients who survive for 2 years or more without tumour recurrence after transhiatal resection for oesophageal cancer and gastric tube reconstruction can lead active and satisfactory lives. Although residual symptoms may persist, their overall QoL is in many ways comparable to that of healthy individuals of the same age. Further longitudinal research is needed to investigate the course of

long-term QoL of these patients. Hopefully, their relatively high QoL consolidates during prolonged follow-up.

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Groin hernia repair in Scotland

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Background: The use of mesh for groin hernia repair has dramatically changed the way this common operation is performed. The aim of this study was to survey the methods of groin hernia repair in Scotland and to assess patient satisfaction with the operation.

Methods: Between 1 April 1998 and 31 March 1999 all patients who underwent groin hernia repair in the National Health Service in Scotland were identified. As well as looking at the type of hernia repair performed and postoperative morbidity, patients were sent a Short Form-36 about 3 months after the operation to assess satisfaction and return to normal activity.

Results: Information was obtained on 5506 (97 per cent) of patients who underwent groin hernia repair during the study period. Eighty-five per cent of patients had an open mesh repair and 4 per cent had a laparoscopic repair. Most operations (85 per cent) were performed using general anaesthesia on an inpatient basis (78 per cent), and 8 per cent were for repair of a recurrent hernia. Potentially serious intraoperative complications were rare (seven patients), although they were significantly ($P < 0.001$) more likely to be associated with a laparoscopic approach or repair of a femoral hernia: relative risk compared with open inguinal hernia repair 33 (95 per cent confidence interval (c.i.) 6–197) and 22 (95 per cent c.i. 3–152) respectively. Wound complications were common and 10 per cent of patients required a district nurse to attend the wound. Patients expressed a high degree of satisfaction; 94 per cent would recommend the same operation to someone else if required.

Conclusion: An open mesh repair using general anaesthesia has become the repair of choice for a groin hernia in Scotland. Despite a high incidence of wound complications, patients are satisfied with this operation.

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Introduction

Hernia repair is one of the most common operations performed in general surgery. The use of mesh popularized by Lichtenstein¹ and colleagues for primary inguinal hernia has dramatically changed the manner in which this common operation is performed. Mesh has been applied in various forms, as a patch or a patch and plug with or without suture fixation. The fact that these procedures are performed without tension has led to assertions that they have significant advantages over conventional methods of repair. There is, however, little evidence from randomized clinical trials to support claims of reduced postoperative pain, more

rapid return to normal activity or a reduced risk of subsequent recurrence.

The aim of this study was to examine the methods of repair performed in the National Health Service (NHS) in Scotland for all types of groin hernia in adults. Short-term outcome from these operations and patient satisfaction with the hernia repair were also assessed.

Patients and methods

Between 1 April 1998 and 31 March 1999 data were gathered on patients who underwent groin hernia repair in the NHS in Scotland, with the exception of the remote islands of Orkney and Shetland. Children or adolescents under 18 years old who underwent hernia repair were not included in the study. Data were collected by local audit

The Editors have satisfied themselves that all authors have contributed significantly to this publication

facilitators in each hospital and by two research nurses funded for the project. Patients were identified from diagnosis (International Classification of Diseases; ICD) and procedure (Office of Population Censuses and Surveys (OPCS) 4) codes, and individual case notes were retrieved to obtain required information. Information was first entered on a patient pro forma and then on to a database, and included such factors as length of time on the waiting list, type of hernia repair, grade of operator and postoperative morbidity. Before the start of the study all consultant surgeons concerned had agreed to participate in the study.

Approximately 3 months after operation all patients were sent a questionnaire to assess their short-term outcome and satisfaction with the operation. This questionnaire was similar to a previously modified Short Form-36 that was used successfully in a large prospective randomized trial to evaluate laparoscopic hernia repair². In addition to standard questions about patient satisfaction and return to normal activities, patients were asked about wound complications and whether or not they received antibiotics after surgery. To estimate any resource implications of postoperative complications, patients recorded whether the district nurse was required to attend the wound and how many general practice and surgical outpatient visits they had made.

Statistical analysis

All data are expressed as median values with interquartile ranges (i.q.r.). Data were analysed by means of a χ^2 test with Yates' correction. Where appropriate, relative risk (RR) was expressed with 95 per cent confidence intervals (c.i.).

Results

A total of 5649 patients underwent hernia repair in the 35 NHS hospitals surveyed in Scotland over the 12-month period. Information was obtained on 5506 (97 per cent) of these, of whom 4062 (74 per cent) returned questionnaires. From the time of the surgical outpatient visit, patients were on the waiting list for a median of 87 (i.q.r. 42–148) days before operation. The median hospital stay for all patients was 2 (i.q.r. 1–3) days. Twenty-five per cent of hernia repairs were planned as day cases, but this was achieved in only 22 per cent. All hospitals apart from two performed day-case hernia repair; the rate of day-case repair varied between 1 and 60 per cent for the different hospitals (*Fig. 1*). Only 6 per cent of patients had a hernia repair under local anaesthesia, while 85 per cent had a repair under general anaesthesia. The remainder were performed under either spinal or epidural anaesthesia. The grade of the principal operator is shown in *Table 1*.

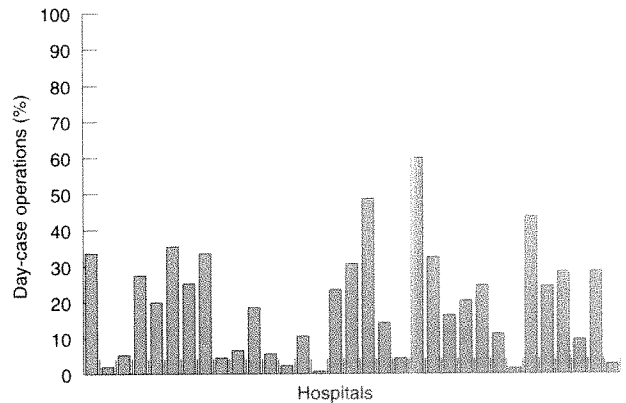


Fig. 1 Percentage of patients operated on as a day case for each hospital

Table 1 Demographic details and grade of principal operator

	No. of patients
Men	5124 (93)
Women	332 (7)
Median (i.q.r.) age (years)	60 (46–71)
Emergency admission	294 (5)
Hernia type*	
Primary inguinal	5225
Recurrent inguinal	446 (8)†
Primary femoral	229
Recurrent femoral	6 (3)†
Surgeon grade	
Senior house officer	1017 (18)
Staff grade	381 (7)
Associate specialist	169 (3)
Specialist registrar	1802 (33)
Consultant	2157 (39)

Values in parentheses are percentages unless stated otherwise. *Includes bilateral hernias. †Expressed as a percentage of all inguinal ($n = 5671$) or all femoral ($n = 235$) hernias. i.q.r., Interquartile range

Prophylaxis of infection and deep vein thrombosis

Seventy-one per cent of patients received prophylactic antibiotics, while 46 per cent had subcutaneous heparin as prophylaxis for deep vein thrombosis (DVT). There was no difference in the rate of wound infection (8 per cent) between those who received prophylactic antibiotics and those who did not: RR 0.9 (95 per cent c.i. 0.7–1.1). Six of 2554 patients who received prophylactic subcutaneous heparin had DVT or pulmonary embolus diagnosed, whereas only one of 2950 who did not have prophylaxis had a diagnosis of DVT ($P = 0.03$): RR 1.8 (95 per cent c.i. 1.4–2.5). One patient developed thrombocytopenia after operation, thought to be related to heparin allergy. Patients who received subcutaneous heparin were significantly

Table 2 Type of hernia repair

	All hernias	Primary inguinal hernia		Bilateral*	Recurrent	Femoral
		< 30 years	≥ 30 years			
Open non-mesh	600 (11)	80 (19)	252 (6)	40 (10)	41 (9)	187 (80)
Open mesh	4612 (84)	331 (77)	3613 (90)	283 (71)	339 (76)	46 (20)
Open preperitoneal	65 (1)	1 (0)	1 (0)	37 (9)	25 (6)	1 (0)
Laparoscopic	229 (4)	17 (4)	131 (3)	39 (10)	41 (9)	1 (0)
Total	5506	429	3997	399	446	235

Values in parentheses are percentages. *Sixty-three per cent of bilateral hernias

($P=0.001$) more likely to develop a wound haematoma (10 *versus* 5 per cent): RR 1.3 (95 per cent c.i. 1.2–1.4).

Type of hernia repair

The type of hernia repair performed for primary, recurrent and bilateral inguinal hernias as well as femoral hernia is listed in *Table 2*. There was a significant ($P<0.01$) trend not to use mesh in patients under 30 years of age. There was a significant ($P<0.01$) trend towards either laparoscopic or open preperitoneal repair for patients with bilateral and recurrent hernias (*Table 2*). The type of primary repair performed was not known for 24 per cent of recurrent hernias; 59 per cent of patients had had a previous open non-mesh repair, and 17 per cent a previous mesh repair.

Complications

Seven potentially serious intraoperative complications occurred (*Table 3*), which included three vascular injuries (two femoral vein, one epigastric artery), two bladder injuries and two small bowel injuries. Three of these were in patients undergoing laparoscopic hernia repair (RR *versus* open inguinal repair 33 (95 per cent c.i. 6–197), $P<0.001$). Two potentially serious intraoperative complications occurred during femoral hernia repair (RR *versus* open inguinal repair 21 (95 per cent c.i. 3–152), $P<0.001$). Nine patients died after operation in hospital or within 30 days of hernia repair; causes included cardiovascular (three patients), advanced cancer (two), sepsis (two) and cause unknown (two).

Response to questionnaire

In all, 4062 patients returned a questionnaire; when asked whether they would recommend the same operation to someone else, 94 per cent replied positively. Ten per cent of patients required a district nurse to attend the wound after operation, and 8 per cent had an antibiotic prescribed. Patients who developed a wound haematoma were sig-

Table 3 Complications

	No. of patients
Operative	
Visceral injury	4 (0)
Vascular injury	3 (0)
Postoperative	
Wound haematoma	378 (7)
Wound infection	431 (8)
Urinary retention	129 (2)
Chest infection	45 (1)
Myocardial infarction	4 (0)
DVT or pulmonary embolus	7 (0)
Other*	37 (1)

Values in parentheses are percentages. *One-third were cardiovascular related; persistent wound pain and numbness were responsible for most of the remainder. DVT, deep vein thrombosis

Table 4 Time to return to normal activities

Activity	No. of patients	Time (days)
Paid work	1534	33 (17–50)
Work in the home	3170	14 (7–28)
Social activity	3494	14 (7–28)
Sexual activity	2075	21 (14–35)

Values are median (interquartile range)

nificantly ($P<0.001$) more likely to report a wound infection than those who did not have a haematoma. Three per cent of patients had severe or very severe groin pain present most or all of the time 3 months after hernia repair. Groin numbness was reported by 9 per cent of patients. The time to return to work and normal activities is shown in *Table 4*.

Discussion

This study demonstrates that almost 90 per cent of patients undergoing groin hernia repair in Scotland have a mesh repair. Open tension-free repair has become the repair of

choice, whereas 4 per cent of patients have a laparoscopic repair. Most repairs are performed using general anaesthesia on an inpatient basis. Serious postoperative complications are rare, but wound morbidity such as haematoma or infection is common. Despite this, most patients were satisfied with the operation and 94 per cent would recommend the same operation to someone else if required. Patients returned to paid employment a median of 33 days after hernia repair, and return to other activities occurred approximately 2 weeks earlier.

A similar attempt to look at hernia repair on a national basis has been undertaken in Sweden³, where a voluntary hernia register has been in place since 1992, and more recently in Denmark⁴. In both countries there is an increasing trend for surgeons to perform an open mesh repair. In both countries the operation is more likely to be undertaken as a day-case procedure under local or regional anaesthesia, such procedures accounting for about 50 per cent of all cases. Approximately 16 per cent of operations in both countries are for recurrent hernias, compared with 8 per cent in Scotland. The reasons for this difference are unclear, but the presence of a consultant or surgeon of another senior surgical grade at more than 95 per cent of operations in Scotland may be a factor. Another possible explanation might be the higher rate of mesh repair in Scotland (90 *versus* 30–50 per cent).

There has been little evidence for or against the use of DVT prophylaxis in hernia repair, but only one of 2950 patients who did not have prophylaxis developed a DVT or pulmonary embolus in the present study. This compares with six of 2554 who had DVT prophylaxis and who developed such a complication. Although this represents a significant difference, the likely explanation is that some surgeons will have prescribed prophylaxis for high-risk patients only. The significant increase in wound haematoma in patients who received subcutaneous heparin (10 *versus* 5 per cent in this study) suggests that this form of DVT prophylaxis should be used only in patients at high risk of developing this complication when undergoing hernia repair.

While most patients received antibiotic prophylaxis, wound infection rates were high irrespective of antibiotic use. There are few randomized clinical trials to guide practice in this area. Platt *et al.*⁵ concluded that antibiotic prophylaxis with a cephalosporin is useful for herniorrhaphy on the grounds that patients who received antibiotic prophylaxis were significantly less likely to require antibiotic treatment after operation. Patients were also less likely to require incision and drainage of an infected wound, although there was no significant difference in the rate of wound infection between the groups.

Despite the fact that open mesh repair can be easily accomplished using local anaesthesia, only 6 per cent of hernias were repaired in this manner in the present study. Local anaesthesia is particularly suitable for day-case hernia repair and has obvious economic advantages over inpatient repair with general anaesthesia. Reluctance among surgeons to perform local anaesthetic repair is surprising as relatively simple modifications to the same technique performed under general anaesthesia, such as gentler handling of tissues and more sharp dissection, allow the procedure to be undertaken with minimal or no discomfort to the patient.

Most hernias, apart from femoral hernias, were repaired using an open mesh technique. Use of mesh in patients under 30 years old with an indirect hernia and a normal transversalis fascia is probably unnecessary⁶ and may expose the patient to potential long-term complications⁷. Likewise, laparoscopic hernia repair is suitable for patients with recurrent and bilateral hernias, with the open preperitoneal approach being reserved for a conversion from laparoscopic surgery.

The high rate of potentially serious complications after laparoscopic hernia repair supports the findings of the Medical Research Council trial set up to evaluate laparoscopic hernia repair². The significant increase in these complications compared with open inguinal hernia repair suggests that this operation should be performed not only for the selected cases mentioned but also by individuals who have considerable experience with the technique.

While this study suggests a satisfactory outcome for hernia repair in the NHS in Scotland, improvements are required. Among these is a need to increase the rate of outpatient hernia repair using local anaesthesia. Wound complications should be reduced by using subcutaneous heparin as DVT prophylaxis only in high-risk patients. Patients with recurrence after anterior repair should be considered for laparoscopic or open preperitoneal repair, and more young adults should have a non-mesh repair. Institution of these targets requires strict guidelines for hernia repair in adults, audit after introduction and a commitment to improving the standard of care for patients with a groin hernia in the NHS.

Acknowledgements

The authors acknowledge the contribution made by the audit facilitators in each hospital who helped with this study and all consultant surgeons in Scotland who perform hernia repair, without whom this study would not have been possible. This work was supported by a grant from the Clinical Resource and Audit Group, Scottish Office.

Future of laparoscopic inguinal hernia surgery

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Introduction

Despite recurrence rates below 1 per cent with open mesh repair^{1,2}, laparoscopic repair has been promoted as having significant advantages. A comprehensive review³ suggests that laparoscopic repair is less painful and recovery quicker. However, a randomized comparison⁴ reported more recurrences and complications after laparoscopic repair. The published evidence is inconclusive.

The current views of surgeons undertaking hernia repair, in the light of this inconclusive evidence, are crucial as the implications for the provision of hernia services, if laparoscopic surgery became the preferred option, would be significant. To establish the current viewpoint, a postal survey was conducted to determine current operative practice, attitudes to laparoscopic repair and opinion as to its likely future role.

Methods

A postal questionnaire was sent in August 1999 to 500 UK-based consultant general (including subspecialties) surgeons. Completion required circling responses to seven questions, although provision for adding free text was made.

Results

Some 374 surgeons responded (74.8 per cent) of whom 340 currently perform hernia repair. Tension-free open mesh techniques are preferentially used by 261 respondents (76.8 per cent) for primary hernia repair, Shouldice repair by 19 (5.6 per cent) and laparoscopic repair by 17 (5.0 per cent). The remainder use combinations of mesh, Shouldice, laparoscopic, Bassini, plug and darn techniques.

A quarter of respondents (87) currently perform laparoscopic repair: 28 for primary repair and 59 only for recurrent or bilateral repair. Forty-two of these 87 favour a transabdominal approach and 32 an extraperitoneal technique; 13 were undecided. A further 87 have ceased performing laparoscopic hernia repair for the reasons shown in *Table 1*. Half of the survey group have never undertaken laparoscopic repair.

Two hundred and twenty-three (65.6 per cent) of the 340 respondents think it unlikely or very unlikely that laparoscopic repair will become the standard technique; just 26 (and only 15 of the 87 current laparoscopists) think it likely or very likely. Some 133 respondents (39.1 per cent) would cease to repair hernias if the laparoscopic technique became the accepted primary repair technique. While 85 per cent of respondents currently performing recurrent or bilateral laparoscopic repair only would extend their practice, only 55 of the 87 who have ceased to perform laparoscopic repair would recommence.

Discussion

A Royal College of Surgeons' review of groin hernia surgery³ suggests that laparoscopic repair gives less post-operative pain, a faster recovery, and similar recurrence and complication rates to open repair. The Medical Research Council (MRC) Laparoscopic Groin Hernia Trial Group⁴ concluded that, although laparoscopic repair has advantages, safety concerns make open repair more appropriate for general surgeons. Notably, all seven recurrences in 928 patients followed laparoscopic repair; all three serious complications occurred during transabdominal laparoscopic repair. A commentary on the MRC paper⁵ condemned the transabdominal technique, but British surgeons do not agree; this survey shows that it remains the favoured technique.

Open mesh repair has gained rapid acceptance. Other techniques (excepting Shouldice and laparoscopic repair) are close to obsolescence. That so few surgeons repair primary hernias laparoscopically is not due to unfamiliarity as half have performed laparoscopic repair. However, half of these have discarded it, and it is noteworthy that clinicians

Table 1 Reasons cited for stopping laparoscopic hernia repair by the 87 respondents who no longer provide a laparoscopic service

Reason	No. of respondents
Cost	28 (32)
Complications	28 (32)
Technique had no benefit	18 (21)
Perceived increase in operating time	14 (16)
Recurrence rate	10 (11)
Need for general anaesthetic	7 (8)
Additional reasons*	14 (16)

Values in parentheses are percentages. *Need for a consultant to perform the procedure, inadequate outcome data, port-site hernias, technical difficulties and the length of the learning curve: implications for teaching. In one unit there were three deaths in 2 years in patients undergoing laparoscopic repair, and one Trust would not indemnify against laparoscopic repair.

are equally worried about costs and complications, and more worried about costs than other clinical disadvantages.

Laparoscopic hernia repair has a tenuous foothold in current practice; this survey suggests that this is unlikely to change.

Acknowledgements

The authors are grateful to AutoSuture for financial support in producing and distributing the questionnaire.

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The Seldinger technique for difficult transurethral catheterization: a gentle alternative to suprapubic puncture

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Introduction

Monitoring of urinary output is a necessity for various surgical procedures. Difficult or unsuccessful transurethral catheterization may lead to iatrogenic urethral lesions which can compromise an otherwise excellent surgical result, frequently causing long-term morbidity with subsequent urological procedures. An endoluminal catheter technique, a less invasive alternative to suprapubic bladder drainage, has been developed and used in 21 patients in whom difficulties with transurethral catheterization were encountered.

Technique

The modified Seldinger technique was applied in 21 patients of mean(s.d.) age 72(8) years who underwent a cardiovascular procedure and in whom difficulties with transurethral catheterization were encountered immediately before operation, which was as follows: coronary artery bypass grafting (six patients), endovascular abdominal aortic aneurysm repair (five), peripheral arterial reconstructive surgery (seven), aortic valve replacement, implantation of an internal cardioverter defibrillator and placement of a DeBakey left ventricular assist device (one patient each).

As transurethral catheterization could not be achieved in these patients, the modified Seldinger technique was applied as described below. The urethra was carefully lubricated and anaesthetized (Instillagel; Farco-Pharma, Cologne, Germany) and an atraumatic 0.035-inch J guidewire, length 30 cm, was inserted through the external urethral opening and moved gently forward into the urinary bladder. A central venous catheter (Seldiflex 6F-2L; Plastimed, Saint Leu La Forêt Cedex, France) or a balloon catheter (paediatric Folsyl 6F catheter; Porgès, Le Plessis Robinson Cedex, France), used in paediatric urology, with the tip cut off, was then advanced over the previously placed guidewire (Fig. 1). The guidewire was removed, urine was aspirated and the catheter connected to the urimeter and fixed with drapes.

The urinary catheter was placed successfully in all patients, although in five patients two or more careful attempts (mean(s.d.) 2.5(2)) were necessary to advance the guidewire into the urinary bladder. Nevertheless, the mean(s.d.) overall time needed for the entire procedure was only 3(2) min. The catheters remained in place for 2(0.5) days. Haematuria, false passages, bladder infection and urinary retention were not observed.

Discussion

Prostatic enlargement leading to urethral stenosis is found in approximately 55–90 per cent of men aged 60–90 years. Only 20–50 per cent of these patients present with clinical signs¹, so that difficulties or failure of transurethral catheterization are encountered frequently before operation. Usually, suprapubic bladder catheterization is advised in this situation². However, bleeding into the urinary bladder may occur³ and produce tamponade, especially in surgical procedures that are inherently associated with perioperative coagulation disorders or the need for immediate postoperative anticoagulation. In addition, postoperative urinary complication may be extremely troublesome after an otherwise successful operative procedure^{4,5}.

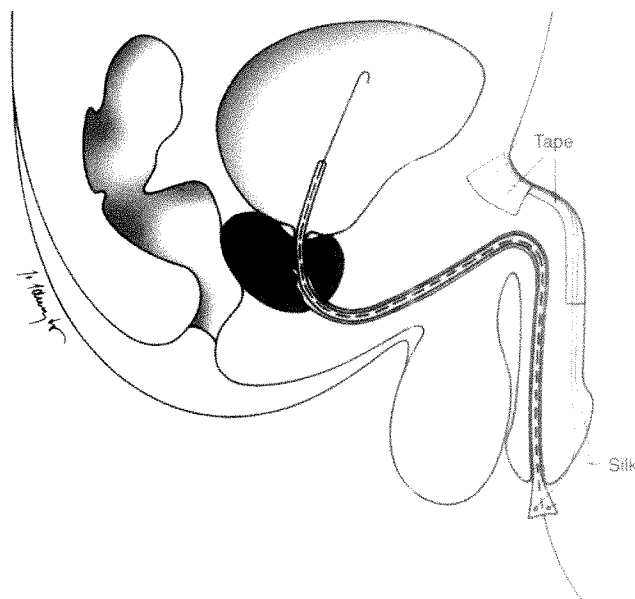


Fig. 1 A guidewire is inserted through the external urethral opening and carefully pushed forward through the urethra. A paediatric Foley (with the tip cut off) or central venous catheter is then pushed forward over the guidewire into the bladder. In the case illustrated, the central venous catheter was fixed with silk passed through the fixation holes of the catheter and taped on to the ventral side and base of the penis.

The Seldinger technique has been developed for peripheral and central venous or arterial catheter insertion. Atraumatic wires with smooth tips may be passed and used to treat even high-grade vascular or endoluminal stenosis. The modified Seldinger technique for difficult urinary catheterization, as described here, is atraumatic, safe, fast and easy to perform, even in patients with unexpected high-grade urethral stenosis, for example from prostatic enlargement.

The perioperative placement of a small-sized catheter by means of the Seldinger technique is a gentle alternative to suprapubic bladder drainage when standard transurethral catheterization is difficult or impossible to perform. If a false passage is suspected, the radio-opaque wire could be introduced under fluoroscopic guidance.

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BJS and the blitz

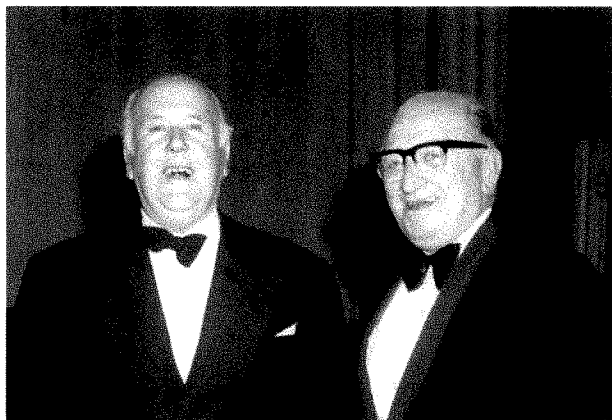


Fig. 1 Leslie Owens with Sir Cecil PG Wakeley. Royal College of Surgeons of England Dinner, 1972

The leading article '*BJS* in the new millennium'¹ observed that publication of the Journal had continued without interruption since July 1913. This simple fact recalls a patient of mine who bore a heavy responsibility for maintaining medical publishing from John Wright and Sons Ltd, publishers of *BJS* during the 1939–45 war. I refer to Leslie George Owens (born 1903), a Bristol science graduate.

Stone-Bridge House, Wright's publishing and printing works, lay in the centre of Bristol and survived many of the night blitzes which began on 24 November 1940. However, the raid on the night of Good Friday (11 April 1941) – which I remember well – completely destroyed the premises. Leslie Owens, at that time an editor but not yet a director of the organization, organized the retrieval of soaked records from a flooded cellar, salvaged printing machines, located others second-hand and borrowed 'space' from several fellow master printers in Bristol, Weston super Mare and Bath. Publication of medical texts in general and *BJS* in particular continued, but it was a close call and an exacting undertaking, especially when the Weston super Mare premises were also destroyed in a raid on 29 June 1942. Leslie's monumental efforts were recognized on his retirement in 1972. A presentation and dinner were arranged for him at the Royal College of Surgeons of England to celebrate his contribution to *BJS*; it was a perceptive and fully justified honour (*Fig. 1*).

I first examined Leslie in 1987 for a parotid problem: it was a robust encounter following which he rejected surgery. He returned in 1997 and has attended regularly since then, escorted by his caring daughter, Helen. For a late nonagenarian (he is now 97), his recall of events and people is astonishing, so we had many revealing discussions concerning such distinguished surgeons as Lord Moynihan, Hey Groves (original *BJS* secretary), Sir Cecil Wakeley, Hamilton Bailey, Robert Milnes Walker and many others. Although slightly frail, Leslie's tremendous character and self-assurance shines through. He was not defeated by the dire events of the 1940s and is worthy of our remembrance for his talent, effort and perseverance. The *BJS* Editorial Committee acknowledged the unflinching determination of the John Wright staff in those dark days²; Leslie was a member of that 'band'.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Management of liver trauma

Sir

We would agree that Parks *et al.* (*Br J Surg* 1999; **86**: 1121–35) should be congratulated on an excellent review of liver trauma. We would also agree with Bramhall and Buckels (*Br J Surg* 2000; **87**: 519–20) that transfer to a hepatobiliary unit for management of complex liver trauma should be considered.

We have slight reservations with Bramhall and Buckels' conclusions about the use of computed tomography (CT) alone in all patients with trauma. Their experience of 43 patients in 8 years represents a highly selected group. The advantages of abdominal ultrasonography are that it is rapidly available and the equipment can be taken to the patient, even in the resuscitation bay. It may be used to exclude the presence of free fluid and to identify renal or splenic trauma.

We have reported our experience of abdominal ultrasonography in a group of 220 severely injured patients with blunt abdominal trauma over a 3-year period, showing an 89.1 per cent sensitivity after repeated scanning and 99.5 per cent specificity. The sensitivity and specificity in a further group of 227 non-severely injured patients were 95 and 100 per cent, respectively¹.

Rapid infusion spiral CT can be regarded as a 'gold standard' for the investigation of abdominal trauma, but where its use is either inappropriate or probably unnecessary ultrasonography may be of great value.

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Exercise training and peripheral vascular disease

Sir

We read with interest the review by Tan *et al.* (*Br J Surg* 2000; **87**: 553–63) of physiological adaptations to exercise training in patients with peripheral vascular disease. However, there remains a further normal peripheral physiological adaptation to training that has not been mentioned.

Exercise training in healthy individuals leads to an enhanced capillary supply to the trained muscle¹. This allows an enhanced capillary transit time and a decrease in the diffusion path length for oxygen from the blood². Intermittent hypoxia is one of the proposed mechanisms underlying this angiogenic response³. Improvements in capillary supply have been demonstrated in healthy subjects training in hypoxic conditions³ and in animal models of peripheral vascular disease in response to exercise training⁴. Such an adaptation could help account for the increase in peak oxygen consumption seen following an exercise training programme in claudicants².

Unlike improvements in cardiac function, an improvement in capillary supply would not necessarily result in improved limb blood flow, as the resistance vessels determining blood flow lie proximal to the capillary bed². Indeed an enhanced capillary supply to type II A fibres has been demonstrated as one of the chronic changes to skeletal muscle in patients with intermittent claudication⁵. There are no reports in the literature on the effects of exercise training on capillary supply in this population.

The authors have highlighted the multifactorial physiological adaptations to exercise training. There remains uncertainty as to the importance of central and peripheral physiological adaptations in this response.

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Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids

Sir

We congratulate Drs Misra and Parshad (*Br J Surg* 2000; **87**: 868–72) for their randomized controlled trial comparing micronized purified flavonoid fraction (MPFF) with placebo in

the control of haemorrhoidal bleeding. The effectiveness of MPFF confirms our own recently published randomized controlled study¹. Therefore, MPFF should be considered a suitable treatment option especially when medical practitioners are not trained (for example, family physicians) or not equipped to perform office procedures (for example, rubber band ligation) safely. However, it must be emphasized that due care must always be exercised in excluding other more dangerous causes of rectal bleeding such as rectal cancer.

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Preoperative staging of rectal cancer allows selection of patients for preoperative radiotherapy

Sir

Horgan and Finlay (*Br J Surg* 2000; 87: 575-9) conclude that preoperative radiotherapy can be omitted in patients with rectal cancer without locally advanced disease if total mesorectal excision (TME) is performed. The quoted leak rate of 2.7 per cent is incorrect given that three of 88 or 3.4 per cent of completed anastomoses had clinical leaks. This is compared to Heald's TME leak rate of 16.5 per cent¹, although TME was performed in only 44 of 114 patients. It is unclear how many leaks occurred in such patients and the leak rate could be up to 6.4 per cent, closer to Heald's actual leak rate of 11 per cent clinical plus 6.4 per cent radiological². No details are provided regarding subclinical radiographic leaks. No information is provided regarding the precise level of the tumour, the proportion of patients who had a defunctioning stoma for higher anastomoses and which groups were assessed by computed tomography or examination under anaesthetic. The eight patients in whom no staging was performed should have been excluded altogether. Low tumours treated by TME, stapled anastomosis and defunctioning stoma clearly represent a different group to the handsewn high anastomoses in terms of leak rate and recurrence, and these should have been studied independently. This is particularly the case for tumours within 5 cm of the anal verge for which the leak rate is 6.5 times higher³. We should await the results of the prospective Medical Research Council CRO7 trial before changing clinical practice.

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- 1 Heald RJ, Karanjia ND. Results of radical surgery for rectal cancer. *World J Surg* 1992; 16: 848-57.
- 2 Karanjia ND, Corder AP, Beam P, Heald RJ. Leakage from low stapled anastomosis after mesorectal excision for carcinoma of the rectum. *Br J Surg* 1994; 81: 1224-6.
- 3 Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg* 1998; 85: 355-8.

Authors' reply

Sir

In our manuscript we described the outcome for a consecutive series of patients with rectal cancer and this was similar to that reported by Heald's group. We were concerned that the use of total mesorectal excision (TME) for the treatment of high rectal tumours would leave a long devascularized rectal tube with a high risk of anastomotic dehiscence. In our series patients with high rectal tumours did not have TME while those with low rectal tumours had a double stapled proctectomy and colorectal anastomosis (TME without leaving devitalized bowel). While accepting that we did not look for radiological leaks, our comparison was not only reasonable but was one of the major reasons for reporting the results of our surgical strategy since it shows that the principles of TME can be adopted at approximately one-quarter of the clinical leak rate without compromising cure.

The remaining information is contained within the Patients and methods section of the manuscript. For example, when referring to higher tumours it was stated that 'Intestinal continuity was then achieved by a single-layer interrupted handsewn anastomosis without a covering ileostomy'. We disagree that the eight patients who were not staged should have been excluded. It is a basic principle that all patients should be included since it allows readers to draw their own conclusions based on the presented data.

We also await the results of the prospective MRC CRO7 trial with interest, but these will not detract from our message because the MRC CRO7 trial makes no allowance for stage of disease. Consequently many patients will receive potentially harmful radiotherapy who do not need it. We highlight the fact that preoperative staging allows the identification of those patients with rectal cancer who are at high or low risk of local recurrence after surgery. Radiotherapy can then be targeted at the high-risk group. It certainly should not be used to compensate for poor surgical technique in the low-risk group. Above all, our data suggest that new trial protocols are required.

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Population screening reduces mortality rate from aortic aneurysm in men

Sir

As a vascular surgeon and epidemiologist I find it very difficult to agree with the conclusions of Heather *et al.* (*Br J Surg* 2000; 87: 750–3) about the reduction in mortality rate from aortic aneurysm as a result of population screening and the effectiveness of a screening programme. Although the reasoning in the article seems logical there is a danger of wrong interpretation by those who are not familiar with the modern design of studies evaluating the effect of screening programmes¹. It should be realized that one of the basic side-effects of a screening programme is the harm to the patient². For aneurysm screening this is, of course, death from elective operation but also major complications such as myocardial infarction, neurological complications, long-lasting postoperative physical impairment, psychological strain, etc. In this study the harmful effects of screening are insufficiently balanced against the benefits. It might even have been that the screening programme in the Gloucestershire area did more harm than good.

The real answer as to whether screening might be effective has to come from a properly conducted randomized trial in which all aspects of a screening programme should be carefully studied and weighed in the analysis.

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- 1 Muir Gray JA. Making decisions about health services. In: Muir Gray JA, ed. *Evidence Based Health Care. How to Make Health Policy and Management Decisions*. New York: Churchill Livingstone, 1997: 29–57.
- 2 Thornton H, Baum M. 'Should a mammographic screening programme carry the warning: screening can damage your health?' *Br J Cancer* 1999; 79: 691–2.

Authors' reply

Sir

Thank you for the opportunity to respond to Dr Legemate's comments, which really apply to the whole concept of elective repair of asymptomatic aortic aneurysms, rather than to screening alone. The reduction in overall mortality from all aneurysm-related causes demonstrated in our paper did, of course, include any small adverse effect from increased operative mortality. We are certainly aware of the potential for any health screening process to cause anxiety, although this seems to be negligible in the 95 per cent of men who can be reassured of a normal aortic diameter. All major surgery may

cause non-fatal complications or long-term morbidity and we would not wish to deny the importance of considering (and striving constantly to improve) overall quality of life outcomes in patients undergoing elective aneurysm repair. Indeed, in the type of randomized controlled trial proposed by Dr Legemate, it is not difficult to predict that more patients offered screening would undergo elective aneurysm surgery and, as a result, might show some decline in at least some life quality criteria. However, significantly more men in the unscreened control group would die from ruptured aneurysms, which itself has a rather adverse influence on most quality of life measures.

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Effect of liver blood flow and function on hepatic indocyanine green clearance measured directly in a cirrhotic animal model

Sir

We read with interest the article by Jiao *et al.* (*Br J Surg* 2000; 87: 568–74) describing a novel technique for the study of liver physiology. They conclude that 'evaluation of ICG uptake and clearance directly from the liver using NIRS clearly correlates well with liver perfusion and function in this cirrhotic animal model'. Unfortunately this interpretation is not supported by the data presented since the technique of correlational analysis is flawed. The study consisted of two groups of rats, those with normal livers and those with diet-induced cirrhosis. These groups are readily identified as distinct clusters on the correlation graphs of liver blood flow and perfusion *versus* hepatic indocyanine green uptake rate, and the derived correlation coefficients are, therefore, largely spurious. Within the groups there appears to be no clear relationship between these variables. Combining mixed samples from different subgroups in this way is a well recognized source of error when calculating correlation coefficients¹.

We agree that quantification of liver function in the diseased organ would be a valuable adjunct in the selection of treatment options for patients with cirrhosis but the technique reported clearly requires further validation in the cirrhotic subset before its utility can be accepted.

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- Altman DC. Relation between two continuous variables. In: *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991: 277–324.

In-hospital delay in the diagnosis of breast cancer

Sir

I was interested in the study by Jenner *et al.* (*Br J Surg* 2000; 87: 914–19). One point that I could not see mentioned was the possibility that in some patients an apparent delay in diagnosis was actually due to a genuine newly detectable cancer when the previous pathology in the same quadrant of the breast had actually been benign. If we assume that the overall incidence of cancer is one in 500 per annum, then the incidence of breast cancer occurring in one particular quadrant of either breast is one in $500 \times$ one in eight equalling one in 4000 per annum. If we are looking over a 10-year period, then this type of event will occur in one in 400 patients and, if we are following the patients for a median of 5 years, the event will occur in five in 400, i.e. approximately one in 100 of the study patients. Therefore, in the study it is possible that ten patients developed breast cancer in a quadrant of the breast where there had previously been no pathology.

I do not think this changes the overall thrust of the paper. Triple assessment with clinical examination, mammography and cytology does give a small but unacceptable risk of missing cancer and in our unit all patients with a breast lump are now assessed with clinical examination, immediate ultrasonography, mammography if the lesion is non-cystic, then ultrasonographically-guided fine-needle aspiration and core biopsy. We are presently evaluating aspects of the efficacy of this system.

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Randomized clinical trial of laparoscopic *versus* open fundoplication: blind evaluation of recovery and discharge period

Sir

We would like to congratulate the authors of this small prospective randomized study (*Br J Surg* 2000; 87: 873–8) for using blinded evaluation to reduce bias. We were disappointed to read that, while the authors acknowledge that the correct way to analyse data from such a study is by 'intention to treat', they in fact analysed the data 'per protocol' in case patients whose operation had to be converted obscured the possible benefit from the laparoscopic approach. They have shown that median hospital stay is the same (although the range made a

statistical difference) and that the laparoscopic approach took significantly longer. Had they included conversions, the laparoscopic group might have fared worse; at least it would have shown no difference. The present method of analysis has unfortunately obscured the clear message of this study – that there is no difference between the two approaches except in operating time.

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Authors' reply

Sir

In the analysis of our study we wanted the results to be as generally applicable as possible. The conversion rate in the small population of the study happened to be higher than in our total group of laparoscopic funduplications. We excluded the converted patients because we did not want the high conversion rate to obscure possible differences. On the other hand the small differences found in the study are probably true only if the conversion rate is low and we acknowledge this in the discussion.

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Long-term results of arteriovenous fistulas using transposed autologous basilic vein

Sir

We read with interest the article by Murphy *et al.* (*Br J Surg* 2000; 87: 819–23) which suggests that a transposed basilic vein to brachial artery arteriovenous fistula has fewer complications and an equal patency rate compared with a prosthetic graft.

Autogenous basilic vein is a better option in patients with no superficial veins as a means of access and we have found it to be a robust alternative. The vein is usually available because it is not used for venepuncture or infusion. We do not routinely perform a venogram preoperatively in the absence of a history of subclavian vein catheterization but often carry out colour duplex imaging of the basilic vein to rule out any stenosis.

We often carry out this procedure in two stages: the first (under local anaesthesia) is fashioning the fistula, with a second

stage 4–6 weeks later transposing and reanastomosing the matured vein under general anaesthesia. This approach has the following advantages: (1) once the vein matures, it is bigger in calibre and therefore technically easier to mobilize; (2) complications such as steal syndrome and venous hypertension can be identified and dealt with before the transposition; (3) if the fistula has a poor flow, fails or is unlikely to be used we do not carry out the transposition, thus avoiding unnecessary dissection and general anaesthetic; and (4) there may also be a better patency rate¹. The disadvantage of doing a two-stage procedure is that a new vascular anastomosis has to be fashioned in a second procedure. Did the authors carry out a staged procedure and, if both methods were used, do they have any data to suggest which is the best technique? A randomized controlled trial would best answer this question.

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- 1 Mallah ES. Staged basilic vein transposition for dialysis angioaccess. *Int Angiol* 1998; 17: 65–8.

Slowing the heart saves lives: advantages of perioperative β -blockade

Sir

We read with interest the leading article by Jones and Powell (*Br J Surg* 2000; 87: 689–90). The evidence that β -adrenoceptor blockade protects against adverse cardiac outcome in non-cardiac surgical patients has appeared relatively recently^{1–4}. However, this concept is not new^{5–7}.

Recent results^{2,3} suggest that there may be a role for β -blockade of high-risk surgical patients, but a number of factors suggest that a more cautious approach needs to be taken: (1) patient characteristics for each study were different – not all had known coronary artery disease, not all underwent vascular surgery and some patients were selected from higher risk groups; and (2) dosing protocols and length of treatment were different in each study. Intravenous administration of the study drug was required in each study with subsequent close monitoring in a high-dependency area. This approach clearly has restrictions for use in the current setting of intensive treatment unit bed availability in the UK.

We can, however, derive some key points: (1) only Poldermans *et al.*² and Raby *et al.*³ studied a high-risk category of patients. If we examine these patients separately, we can find some evidence for benefit (decreased mortality and morbidity) to set against the need for the provision of intensive monitoring facilities; (2) Mangano *et al.*¹ showed no decrease in perioperative death but a decrease in death (from any cause) at 2 years in those given β -blockers; and (3) Urban *et al.*⁴ showed no difference in outcome.

From the available evidence there is little support for the routine initiation of perioperative β -blockade in non-vascular patients, while in vascular patients there is a need for a British outcome study which includes a clear assessment of the cost: benefit ratio for such treatment. The results at present do not confirm β -blockade to be the Holy Grail that is sought by both anaesthetists and surgeons.

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- 1 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; 335: 1713–20.
- 2 Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999; 341: 1789–94.
- 3 Raby KE, Brull SJ, Timimi F, Akhtar S, Rosenbaum S, Naimi C *et al*. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg* 1999; 88: 477–82.
- 4 Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P. Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. *Anesth Analg* 2000; 90: 1257–61.
- 5 Prys-Roberts C, Foëx P, Biro GP, Roberts JG. Studies of anaesthesia in relation to hypertension. V. Adrenergic beta-receptor blockade. *Br J Anaesth* 1973; 45: 671–81.
- 6 Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. *Anesthesiology* 1988; 68: 495–500.
- 7 Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. *Br J Anaesth* 1988; 61: 675–9.

Authors' reply

Sir

We are pleased that Higham *et al.* are supportive of many of the comments made in our leading article and accept that the studies to date have used diverse patient groups and outcome measures. The consequence of this is that no useful meta-analysis can be conducted. It is for this reason that we are supporting the trial of a pragmatic regimen of perioperative β -blockade in patients undergoing vascular surgery. For patients

undergoing major abdominal, orthopaedic or other procedures, stratification using the revised Goldman Cardiac Risk Index¹ could be sufficient to identify those who might benefit from perioperative β -blockade.

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- 1 Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9.

Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review

Sir

Rodgers and McCall (*Br J Surg* 2000; **87**: 1142–55) attempt to address the question of hepatic node involvement in this systematic review and perhaps the only conclusion that can be drawn is that there is lack of adequate data on this subject. Only 15 of 185 studies had any meaningful data on hepatic node

involvement and, of these, only five studies described formal hepatic node dissection (three of these five studies report data on eight, seven and eight patients each). A large multicentre French trial (1818 patients) reported a 12 per cent 5-year survival rate for those with positive nodes ($n = 100$)¹. A recent study by the same group² suggests a definite role for portal skeletonization in patients with limited hepatic (portal) nodal involvement.

Your brief 'one-line' summary in the contents section of the journal describing the findings of this study may be misleading as it states that 'there are few 5-year survivors after liver resection', which is factually incorrect.

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- 1 Nordlinger B, Jaeck D, eds. *Treatment of Hepatic Metastasis of Colorectal Cancer*. Heidelberg: Springer, 1992: 129–46
- 2 Jaeck D, Nakano H, Bachellier P, Weber J-C, Inoue K, Oussoultzoglou E. Data presented at the 7th meeting of the European Surgical Association, Amsterdam, April 2000.

Thyroid Cancer – A Comprehensive Guide to Clinical Management

L. Wartofsky (ed)

185 × 280 mm. Pp. 515. Illustrated 2000 Totowa, New Jersey: Humana Press \$175 00.

Thyroid disease is common but thyroid cancer is rare. The spectrum of malignancy ranges from indolent, for example pure familial medullary thyroid cancer, to one of the most aggressive tumours encountered – anaplastic thyroid carcinoma. As Dr Mazzaferri writes in the foreword, 'because of its low incidence there have been no prospective randomized clinical trials of the treatment of thyroid carcinoma' and 'none are likely to be done, given the prolonged survival and relatively low mortality rates'. Despite this nihilism the book provides a no-nonsense presentation of the disease, with generic introductory sections on diagnosis, pathogenesis, epidemiology, etc., before specific parts which deal with each of the histological subtypes with individual contributions on clinical aspects, pathology, treatment and prognosis. The book brings the reader up-to-date on the latest molecular biology, but how can a textbook remain extant when rates of progress in some areas are significant from month to month? An example would be the understanding of inherited medullary thyroid carcinoma, which has gone from clinical observation in 1959 to our current knowledge of the location and type of mutations and the beginnings of understanding intracellular mechanisms. The diagrams, figures and tables are clear and helpful. There is only one colour figure (showing the intensity of radiation zones around Chernobyl). Colour should have been used for the many illustrations of cytology and histopathology, which lack clarity and can be understood only poorly in black and white. Contributions on surgery come from one internationally recognized thyroid surgeon who is surrounded by 23 other multidisciplinary authors, all of whom are based in America. This is not a surgically based or biased text but it is an excellent starting reference for those surgeons who wish to learn about all aspects of thyroid cancer.

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Classic Papers in Urology

E. W. Gerharz, M. Emberton, T. O'Brien (eds)

282 × 195 mm Pp. 372. Illustrated. 1999 Oxford: Isis Medical Media £39.95

This book offers 150 papers selected by 21 authors from Europe and the United States of America. It covers such diverse topics as Young's original description of posterior urethral valves and the discovery that prostate specific antigen based screening increases the detection of organ confined prostate cancer. Some of the reviews of the classic papers are excellent as they provide a comprehensive précis in addition to the strengths, weaknesses and relevance of the paper. However

there are other reviews that are less comprehensive, where the reader might be forgiven for wondering if the reviewer had even read the original article. This is the sort of book that should appear in the departmental library. Those short of topics for teaching sessions would find plenty of material here. It should stimulate urologists of all ages to re-read many of the seminal papers in urology that have formed the basis for so much of our practice which is now taken for granted.

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Bailey and Love's Short Practice Of Surgery – 23rd Ed.

R. C. G. Russell, N. S. Williams, C. J. K. Bulstrode (eds)

282 × 222 mm Pp 1348. Illustrated 2000. London: Arnold £85.00

The publication of a new edition of a well-established text is always of interest. The reader is keen to know of any innovations in the content and presentation. They are also interested to see which subjects have been retained and which have been omitted. The fundamental principle of Bailey and Love has always been the emphasis on clinical observation and the detection of clinical signs. This edition is no exception and the addition of some excellent clinical colour photographs significantly enhances the descriptions in the text. The primary importance of clinical diagnosis has been supplemented by new chapters on imaging, reflecting the major advances in radiological techniques, and on microbiological methods in surgical practice. The overall layout is largely unchanged and a review of the contents is very familiar to those who know previous editions. There is an interesting additional chapter on surgical ethics, which together with the chapters on audit and clinical trials highlights the importance of these subjects to surgical practice. The editorial team now includes an orthopaedic surgeon, which changes the established general surgical predominance of the past. As a result, the orthopaedic content is more comprehensive. This does, however, raise a question of the targeted readership. In the preface the editors describe the readership as students, surgeons in training and practising general surgeons outside specialist departments. Changes in undergraduate and postgraduate surgical training and examination have resulted in students having different needs. Such needs may not necessarily be met by such a comprehensive text, particularly at undergraduate and higher trainee level. Nevertheless the publishers have managed to minimize costs and this edition does give excellent value as a reference.

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Scientific Surgery

Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *BMJ* 2000; 321: 531–5.

Some 13 trials including 1365 patients were analyzed. Chemotherapy improved survival a median of 3.7 months; evidence relating to quality of life was poor

Van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, van Der Scheuren *et al.* Long term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000; 92: 1143–50.

This was a late follow-up of 868 patients with breast cancer. After 10 years survival rates were similar (66 per cent after mastectomy *versus* 65 per cent after breast conservation), but local recurrence rates were higher after breast conservation (20 *versus* 12 per cent, $P=0.01$)

Luijendijk RW, Hop WCJ, van den Tol P, de Lange DCD, Braaksma MMJ, Ijzermans JNM *et al.* A comparison of suture repair with mesh repair for incisional hernia. *N Engl J Med* 2000; 343: 392–8.

Two hundred patients having repair of a midline incisional hernia were recruited. Mesh repair reduced three-year cumulative recurrence rates from 43 to 24 per cent ($P=0.02$)

Pupelis G, Austrums E, Jansone A, Sprucs R, Wehbi H. Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. *Eur J Surg* 2000; 166: 383–7.

This preliminary report included 29 patients. Mortality was 1/11 who had enteral *versus* 5/18 who had conventional intravenous feeding.

Hendolin HI, Pakkonen ME, Alhava EM, Tarvainen R, Kempinen T, Lahtinen P. Laparoscopic or open cholecystectomy: a prospective randomised trial to compare postoperative pain, pulmonary function and stress response. *Eur J Surg* 2000; 166: 394–9.

Forty-nine patients were studied. Laparoscopic cholecystectomy was associated with a shorter hospital stay (4.5 *versus* 2 days, $P<0.01$), less sick leave, less postoperative pain and better pulmonary function.

Ahmed R, Freeman JV, Ross B, Kohler B, Nicholl JP, Johnson AG. Long term response to gallstone treatment – problems and surprises. *Eur J Surg* 2000; 166: 447–54.

This was a late follow-up including 144 of 179 patients originally randomized to cholecystectomy or lithotripsy five years previously. Some 45 per cent of the lithotripsy patients required cholecystectomy, and this group had the worst functional results

Capussotti L, Vergara V, Polastri R, Bouzari H, Galatola G. Liver function and encephalopathy after partial *versus* direct side-to-side portocaval shunt: a prospective randomized clinical trial. *Surgery* 2000; 127: 614–21.

These two types of portocaval shunts were compared in 46 'good risk' patients with cirrhosis and variceal bleeding. None died. Encephalopathy-free survival was greater in the partial shunt group

Ho Y-H, Tan M, Leong AF, Seow-Choen F. Ambulatory manometry in patients with colonic J-pouch and straight coloanal anastomosis: randomized, controlled trial. *Dis Colon Rectum* 2000; 43: 793–9.

The pouch patients had reduced frequency of defaecation (4.6 *versus* 7.1/day) in this trial including 47 patients. Similarly, ambulatory manometric pressure measurements were more favourable in this group after one year

Slim K, Bousquet J, Kwiatkowski F, Lescure G, Pezet D, Chipponi J. Effect of CO₂ gas warming on pain after laparoscopic surgery: a randomized double-blind controlled trial. *Surg Endosc* 1999; 13: 1110–4.

The effect of warming the gas used for insufflation in this trial of upper abdominal laparoscopic surgery was significantly to increase postoperative subcostal and shoulder-tip pain in this study of 100 patients

Johnson WC, Lee KK and members of the Department of Veterans Affairs COOP Study 141. A comparative evaluation of polytetrafluoroethylene, umbilical vein, and saphenous vein bypass grafts for above-knee revascularization: a prospective randomized Department of Veterans Affairs cooperative study. *J Vasc Surg* 2000; 32: 268–77.

This multicentre trial involved 752 patients. At five years, primary assisted patency was as follows: saphenous vein 73 per cent, human umbilical vein 53 per cent and PTFE 39 per cent. Limb salvage was lower with PTFE

Burger DHC, Kappetein AP, van Bockel H, Breslau PJ. A prospective randomized trial comparing vein with polytetrafluoroethylene in above-knee femoropopliteal bypass grafting. *J Vasc Surg* 2000; 32: 278–83.

Some 136 patients were included. After two years, there was no difference in primary patency (83 per cent vein *versus* 87 per cent PTFE) or secondary patency (83 *versus* 77 per cent, respectively).

Mouton WG, Bessel JR, Millard SH, Baxter PS, Maddern GJ. A randomized trial assessing the benefit of humidifying insufflation gas during laparoscopic surgery. *Surg Endosc* 1999; 13: 106–8.

Humidification did not affect body temperature in the 40 patients randomized. It did, however, significantly reduce postoperative pain (visual analogue score) and the time taken to return to normal activity (5.9 *versus* 10.9 days).

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The *British Journal of Surgery* subscribes to the policy of uniform requirements for manuscripts which facilitates resubmission of papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* (*N Engl J Med* 1997; 336: 309-15), or obtain Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £2.95 per copy).

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Original articles should normally be in the format of introduction, patients and methods, results and discussion. Please provide a 200-word structured abstract. Lengthy manuscripts will be returned for shortening. The discussion in particular should be clear and concise and limited to matters arising directly from the results. Avoid discursive speculation. **Randomized clinical trials** should be clearly identified as such in the title and abstract.

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The Editors commission leading articles that are 600-900 words in length and address controversial topics of current interest. They should be supported by no more than ten key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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Manuscripts must be clearly reproduced with adequate space for editorial notes. Present the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. **Begin each section (abstract, introduction, patients and methods, results and discussion) on a new page. Manuscripts that do not conform to these requirements will be returned for recasting.**

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) **the name, postal and email addresses, telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed;** (5) sources of financial support, and (6) the category in which the manuscript is being submitted (original article, review, etc).

Abstract

This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

Tables and illustrations

Submit four copies of all illustrations and tables. Type each table on a separate page with a brief title. Line drawings are acceptable as clear black on white graphics, computer print-out or photocopies. Submit radiographs, photomicrographs, etc unmounted in the form of glossy prints, original transparencies or negatives. Illustrations in colour are encouraged and will be printed at no cost to the author. If you include photocopies, they should be of sufficient quality to enable the Journal's referees to judge their content and value. Label each illustration on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); indicate the top of the illustration. Include a measure of magnification of photomicrographs. Include explanations of symbols and shading within the figure. Survival curves must be accompanied by a table giving the actual numbers of patients involved. Include in the legends to illustrations and the footnotes to tables brief but comprehensive explanations of all the information presented. Look at recent issues of the Journal for examples of accepted layout. Any table or illustration reproduced from a published work must give the original source in full. You must obtain permission from the original author and the publisher before submission.

Abbreviations

Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension.

Abbreviations must be used consistently and must be defined on first use.

Numbers and units

Use the decimal point, not a comma, for example 5.7. Use a space and not a comma after thousands and multiples thereof, for example 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg).

Statistics

For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782-4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637-9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript¹ or ¹⁻³. References cited only in tables or figures should be numbered in sequence.

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